Advances and Emerging Opportunities in Type 1 Diabetes Research: A Strategic Plan

Developed Under the Auspices of the Statutory Diabetes Mellitus Interagency Coordinating Committee

Version 1—For Patients and the Public

National Institute of Diabetes & Digestive & Kidney Diseases

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SUMMARY AND RECOMMENDATIONS

The Strategic Plan will serve as a scientific guidepost to the National Institutes of Health (NIH) and to the investigative and lay communities by identifying compelling research opportunities that will inform future type 1 diabetes research efforts and propel research progress on the understanding, prevention, treatment, and cure of type 1 diabetes and its complications for the next decade.

OVERVIEW OF TYPE 1 DIABETES

Type 1 diabetes is a devastating disease in which the body's immune system attacks and destroys insulin-producing beta cells, which are found in clusters in the pancreas called islets. Without this vital hormone, the cells and tissues cannot absorb glucose (sugar), and patients' cells can starve to death, despite high levels of glucose in the bloodstream. Therefore, patients require daily insulin administration for survival. Type 1 diabetes, as patients and parents say, "never takes a day off." Patients or caregivers must constantly monitor glucose levels. If they are too high, patients must take insulin. If too low, they must eat food to boost their glucose levels. The constant burden of this disease greatly affects the quality of life of patients and family members.

Although life-saving, insulin therapy is not a cure. Despite the vigilant efforts of patients to keep their glucose levels as close to normal as possible, chronically high glucose levels (hyperglycemia) damage their organs. This damage, in turn, can result in the development of life-threatening disease complications, such as blindness, kidney failure, nerve damage, lower limb amputation, heart disease, and stroke. These complications can reduce average life span by many years. Given the unremitting demands of diabetes, it is not surprising that it heightens the risks for various psychiatric disorders, such as depression. On the flip side, when patients aggressively manage their glucose levels with insulin therapy to try to prevent these devastating complications, they are at risk for dangerous episodes of low blood glucose (hypoglycemia). Patients may not even be aware that they are experiencing these episodes (hypoglycemia unawareness). If left untreated, hypoglycemia can result in coma and even death. Patients with type 1 diabetes must constantly walk a tightrope to balance the risks of the immediate danger of hypoglycemia and the long-term danger of complications from high blood glucose levels.

Type 1 diabetes differs from type 2 diabetes, which is more commonly diagnosed in adulthood, is strongly associated with overweight and obesity, and disproportionately affects minority populations. However, both forms of the disease share the same complications. Treating diabetes and its complications places an enormous public health burden on the United States.

RESEARCH OBJECTIVES

This Strategic Plan identifies key research objectives that will guide future NIH efforts to achieve six overarching Goals of type 1 diabetes research. The objectives outlined in this Plan build upon recent scientific advances and represent scientific opportunities for overcoming current barriers and achieving progress in type 1 diabetes research over the next 10 years.

Goal I: Identify the Genetic and Environmental Causes of Type 1 Diabetes

Type 1 diabetes results from an interplay of genetic and environmental factors. Several key genes involved in the disease have been identified, but many more remain unknown. Environmental factors have also been found to play a role, but no single trigger has been conclusively identified. Research

on genetic and environmental factors could help predict who will develop type 1 diabetes, and could also lead to the identification of novel prevention strategies. Key research objectives in this area are:

Genetic Causes

- Create Resources for the Study of Type 1 Diabetes Genetics
- Identify Human Genes Causing Type 1 Diabetes
- Use Knowledge About the Genetic Underpinnings of Type 1 Diabetes To Prevent and Treat the Disease

Environmental Causes

- Monitor Rates of Type 1 Diabetes
- Assess Environmental Causes of Type 1 Diabetes

Goal II: Prevent or Reverse Type 1 Diabetes

Preventing type 1 diabetes onset would obviate the need for daily insulin administration and the serious disease complications. Research to explore the defects in the immune system that are associated with autoimmunity could lead to new methods to predict, diagnose, treat, and ultimately prevent the disease. In addition, research is required to halt or reverse beta cell destruction after disease onset, to preserve patients' insulin producing capacity. Key research objectives in this area are:

Risk Assessment

- Identify and Optimize the Detection of Immunologic, Genetic, and Metabolic Markers of Type 1 Diabetes

Immunopathogenesis

- Understand the Interplay Between Early Environmental Encounters and the Immunoregulatory Defects That Results in Beta Cell Destruction in Human Type 1 Diabetes
- Advance Basic Understanding of Facets of the Human Immune Response (e.g., Regulatory T Cells, Innate Immunity) That Have Recently Been Appreciated as Key Mediators of Beta Cell Destruction

Clinical Trials

- Identify an Intervention Capable of Long-term Reversal of Recent Onset Type 1 Diabetes Without Concomitant Short- or Long-term Adverse Effects
- Develop a Safe and Universal Means for the Primary Prevention of Type 1 Diabetes

Goal III: Develop Cell Replacement Therapy

Islet transplantation has engendered tremendous hope as a possible cure for type 1 diabetes. This therapeutic strategy replaces the insulin-producing beta cells destroyed by the immune system, thereby eliminating or reducing the need for insulin administration. However, to make this strategy a viable option for most patients, it is imperative to overcome the numerous obstacles that still exist, such as the shortage of available islets and the need for less toxic methods to prevent islet rejection and the recurrence of autoimmunity. Research on both beta cell biology and clinical islet transplantation can help to overcome these and other barriers. Key research objectives in this area are:

Islet Transplantation

- Develop Novel Strategies and Infrastructure That Support Advancing Pancreas Procurement and Islet Processing
- Develop Improved Methods To Assess Islet Beta Cell Viability and Function That Predict Early Islet Function After Transplant
- Investigate the Use of Porcine Islets as an Alternate Source of Islets for Transplantation
- Improve Islet Transplant Procedures
- Develop Novel Methods To Accurately Assess the Post-Transplant Islet Mass
- Harness New Understanding of the Immune System To Develop Improved Clinical Monitoring and Immunotherapies

Pancreatic Development, Stem Cells, and Regeneration

- Grow a Renewable Supply of Pancreatic Beta Cells That Can Be Transplanted into Patients
- Understand How Mature Beta Cells Are Maintained and Replenished in the Adult Pancreas
- Develop Strategies To Regenerate Beta Cells Through Replication or Neogenesis

Goal IV: Prevent or Reduce Hypoglycemia in Type 1 Diabetes

Hypoglycemia is a distressing, acute complication of type 1 diabetes. Low blood glucose impairs brain and other bodily functions, including defenses against future hypoglycemia episodes, causing a vicious cycle of recurrent events. Understanding how the brain and body work together to sense and

adjust glucose levels, as well as research to improve and link glucose monitoring and insulin delivery, could help scientists develop strategies to prevent hypoglycemic episodes and improve patients' quality of life. Key research objectives in this area are:

Brain and Peripheral Nervous System Mechanisms of Hypoglycemia

- Define the Mechanisms and Modulators of Metabolic Sensing
- Elucidate Brain Alterations in Response to Hypoglycemia
- Develop New Strategies To Prevent or Reverse Hypoglycemia-Associated Autonomic Failure

Clinical Interventions To Prevent or Reduce Hypoglycemia

- Control Hypoglycemia Through Behavioral Therapies
- Close the Loop: Develop the Tools Required for an Artificial Pancreas

Goal V: Prevent or Reduce the Complications of Type 1 Diabetes

Persistent elevation of blood glucose can lead to life-threatening disease complications. Research has dramatically demonstrated that intensive control of blood glucose levels can prevent or delay the development of these complications. However, because of the limitations and difficulties of current therapies for achieving good glucose control, as well as the threat of hypoglycemia associated with intensive control, patients rarely achieve recommended glucose levels. Future research strategies will build upon the existing approaches to control diabetes, as well as develop novel approaches to break the link between high glucose and chronic complications. Key research objectives in this area are:

Molecular Mechanisms of Common Pathways in Diabetic Complications

- Identify Molecular Pathways of Hyperglycemia Damage
- Clarify Mechanisms Linking Fuel Utilization and Heart Disease
- Understand the Systems Biology of Diabetic Complications

Metabolic Memory

- Discover the Molecular Mechanisms of Metabolic Memory

Genetic Factors

- Identify Genes Conferring Susceptibility and Resistance to Diabetic Complications

Animal Models

- Develop More Human-like Animal Models of Diabetic Complications

Biomarkers and Surrogate Endpoints To Facilitate Clinical Trials

- Identify Biomarkers or a Combination of Biomarkers for Earlier Detection of Cell and Tissue Damage
- Validate Surrogate Endpoints for Assessing the Progression of Complications in Clinical Trials

Therapies To Improve Patient Health

- Identify Therapeutics That Prevent or Reverse the Development and Progression of Diabetic Complications
- Mitigate Psychosocial Complications and Comorbidities of Diabetes To Improve Quality of Life
- Combine New Technology for Diabetes Management with Behavioral and Translational Research

Goal VI: Attract New Talent and Apply New Technologies to Research on Type 1 Diabetes

Continued research progress depends on attracting and training a workforce of scientists with diverse expertise to conduct research on type 1 diabetes and its complications. In addition, the harnessing of new and emerging technologies sets the stage for innovative discoveries that can bring tremendous benefits to patients. Key research objectives in this area are:

Engaging Talented Scientists

- Recruit Expertise from Diverse Fields
- Design Incentives That Reward Research Innovation
- Train New Scientists in Clinical Type 1 Diabetes Research

Development and Application of New Technologies

- Develop Noninvasive Imaging Technologies To Monitor Type 1 Diabetes
- Promote Application of Advances in Bioengineering to Type 1 Diabetes
- Foster Application of Gene Delivery and Gene Silencing Technology To Develop New Therapies for Type 1 Diabetes and Its Complications
- Apply New and Emerging Technologies in Functional Genomics, Proteomics, and Metabolomics to Type 1 Diabetes Research
- Improve the Power of Diabetes Research by Utilizing Computational Biology and Bioinformatics
- Apply New Technology to the Development of Improved Animal Models for the Study of Type 1 Diabetes

NIH SUPPORT FOR TYPE 1 DIABETES RESEARCH

Research toward achieving the six overarching Goals has been accelerated by the *Special Statutory Funding Program for Type 1 Diabetes Research*. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) administers this special appropriation on behalf of the Secretary of the Department of Health and Human Services (HHS), in collaboration with multiple other NIH Institutes and Centers, and the Centers for Disease Control and Prevention (CDC). The *Special Funding Program* has allowed the creation of unique, collaborative, and innovative research consortia and clinical trials networks to increase understanding about the prevention, treatment, and cure of type 1 diabetes. Initiatives supported by the program are different in size, scope, duration, and nature from other type 1 diabetes efforts supported through regular NIH appropriations. The *Special Funding Program* enabled the initiation of most of these large-scale, high-impact efforts, at a scientifically optimal scale of operation. Importantly, the research efforts that have been supported to date have spurred numerous future opportunities that could dramatically improve the lives of patients with type 1 diabetes. Type 1 diabetes research is also supported by regularly appropriated funds to HHS.

IMPLEMENTATION: GUIDING FUTURE RESEARCH EFFORTS

This Strategic Plan reflects a dynamic planning process that involves collaboration among numerous stakeholders to ensure that research progress is regularly assessed and that new and emerging opportunities are identified. The statutory Diabetes Mellitus Interagency Coordinating Committee will continue to play a key role by assessing progress toward attaining the goals and objectives described in this Plan, which was developed under its auspices. The NIH will also continue to solicit broad external input from the scientific, lay, and patient advocacy communities to inform its planning efforts. The NIH will use the research objectives described in this Strategic Plan as a scientific guidepost to improve current treatment strategies and to identify ways to prevent or cure type 1 diabetes and its complications.

Process for the Development of the Type 1 Diabetes Research Strategic Plan

Origin

One of the recommendations emanating from a January 2005 *ad hoc* planning and evaluation meeting focused on large scale efforts made possible by the *Special Statutory Funding Program for Type 1 Diabetes Research* was that the NIH should initiate a broad review of the entire state-of-the-science with respect to type 1 diabetes and its complications. In response to this recommendation, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) launched a new strategic planning effort for type 1 diabetes research.

Collaborative Planning Process

This Strategic Plan was developed through an open and inclusive planning process, with oversight by the statutory Diabetes Mellitus Interagency Coordinating Committee, and leadership by the NIDDK Division of Diabetes, Endocrinology, and Metabolic Diseases. The Committee, chaired by the NIDDK, includes representation from NIH components involved in diabetes research, as well as from other relevant federal agencies.

To develop the scientific chapters of the Strategic Plan, Working Groups were convened to identify recent scientific advances and research objectives for Goals I-V. Goal VI, "Attract New Talent and Apply New Technologies to Research on Type 1 Diabetes," was addressed by all Working Groups because it is an interdisciplinary goal that applies across type 1 diabetes research. The Working Groups were composed of a diverse and talented group of individuals who are committed to propelling progress in type 1 diabetes research. They were chaired by scientists external to the NIH, with membership that included extramural scientists, NIH representatives, patients, and representatives from patient advocacy groups.

Public comment was solicited prior to publication by the posting of the draft plan on a Web site created for the planning effort (www.T1Diabetes.nih.gov/plan).

Organization of the Strategic Plan

The Strategic Plan was framed around the six overarching scientific goals of type 1 diabetes research. One version of the Plan was developed for patients with type 1 diabetes, their family members, and the public. It contains a description of how research addressing each goal could benefit people living with type 1 diabetes and their family members, as well as profiles of patients and scientists. Another version of the Plan was developed for the scientific research community. While tailored to different readers, both versions highlight key recent scientific advances that have accelerated research and/or benefited patients' health, and identify the most compelling opportunities and objectives for research.

Both versions of the Plan contain a summary of major research objectives. Research objectives are specific research directions that can be pursued over the next decade, within available NIH resources, to realize the goal of each chapter. In some cases, these objectives intersect with one another and may be dependent upon one another for progress. For example, identifying environmental triggers of type 1 diabetes (Goal I) will help to inform future disease prevention strategies (Goal II). Also, "Attract New Talent and Apply New Technologies" (Goal VI) is important for every area of type 1 diabetes research. The Strategic Plan describes a coordinated, multifaceted approach for significantly advancing research to combat type 1 diabetes.

INTRODUCTION

OVERVIEW, BURDEN, AND IMPACT OF DISEASE

This Strategic Plan focuses on type 1 diabetes—the form of the disease in which the body's immune system destroys the cells that produce insulin, a hormone that regulates the amount of glucose (sugar) in the blood and is essential for life. Because patients with type 1 diabetes no longer produce insulin, which is necessary for survival, they require daily insulin administration, either through injections or an insulin pump. In the other major form of diabetes—type 2 diabetes—loss of effective insulin action is due to a combination of defects, both in normal insulin action (insulin resistance) and in the ability of pancreatic beta cells to overcome this insulin resistance by secreting sufficient amounts of additional insulin. Both forms of the disease share the same possible complications, which include blindness, kidney failure, nerve damage, lower limb amputations, heart disease, and stroke.

Type 1 diabetes can be more serious and costly for patients because it tends to strike earlier in life. For example, while type 2 diabetes increases the risk of heart disease 2- to 4-fold (1), heart disease risk is increased by up to 10-fold in patients with type 1 diabetes compared to the general age-matched population (2, 3). Importantly, the longer a person has diabetic complications, the more severe, difficult-to-treat, and costly they can become. Thus, an early diagnosis of type 1 diabetes can set the stage for a lifetime of living with and medically managing the disease complications. Few chronic medical conditions rival type 1 diabetes in terms of the extent to which maintenance of acceptable health is so heavily dependent on the capacity of patients and families to make and execute effective self-management decisions while simultaneously addressing many other complex priorities.

With respect to quality of life, dreaded complications can diminish the vitality of childhood and adolescence, as well as the prime productivity of young adulthood. Patients and their parents often wait anxiously to receive test results of their eye and kidney function. A broken blood vessel in the retina, or the finding of protein in the urine, can be the first sign that a relentless complication of the disease has emerged, and that grueling and costly treatments are in the near future. Even with recent advances in treatment, type 1 diabetes is estimated to lower average life expectancy by 15 years (4). For childhood-onset cases, greater than 15 percent of patients with type 1 diabetes will die by age 40 (4). Thus, early onset type 1 diabetes has major adverse impacts on patients and on society because of its extremely high personal and economic costs.

Type 1 diabetes has much in common with type 2 diabetes despite key differences in the mechanisms underlying development of the two forms of diabetes. Both involve malfunctions in the body's system for maintaining appropriate blood glucose levels due to defects in insulin production. Thus, research to understand the intricacies of insulin-producing beta cells, and to find ways to preserve and restore beta cell function, would benefit all diabetes patients. Similarly, the mechanisms of hypoglycemia (dangerous episodes of low blood sugar that can lead to coma and death) are also common to both forms of the disease and limit the ability to deliver therapy proven to prevent or slow complications. Therefore, research to understand and counteract hypoglycemia's effects on the brain would help those with both forms of diabetes. In the same way, all diabetes patients would gain from research directed toward understanding, treating, and preventing the eye, nerve, kidney, heart, and other complications that type 1 and type 2 diabetes share. Alarmingly, both forms of the disease are being increasingly diagnosed at a younger age,

1901

"Diabetes Mellitus" defined as "destruction of the islands of Langerhans."

1915

"Rainbow test," glucose monitoring with Benedict's Solution, provided an inexpensive way to roughly measure sugar levels in urine.

1921

Frederick Banting and Charles Best "discover" insulin, successfully treating a diabetic dog.

1922

First diabetes patient successfully treated with insulin.

1935

Doctors recognized distinction between type 1 and type 2 diabetes based on "insulin sensitivity."

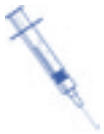
when the disease is more difficult to control; earlier onset increases diabetes' toll in lost health and productivity. Research aimed at diabetes in pediatric populations may help to shed light on and combat this trend. Furthermore, researchers are increasingly recognizing that many patients may have "hybrid" forms of diabetes. Careful characterization of patients considered to have type 2 diabetes reveals that a subset also have markers of type 1 diabetes known as autoantibodies. Interestingly, some patients with type 1 diabetes have the "insulin resistance" that was previously considered a hallmark of type 2 diabetes. Over the past 10 years, evidence has mounted to show that, in type 1 diabetes, high blood glucose levels themselves eventually cause secondary insulin resistance in nearly all patients. These observations are further blurring the line that has historically separated the two forms of the disease. They underscore how research progress on one form of the disease can have enormous benefits for the other form as well.

The interdependence and synergism of research on the two forms of diabetes have been clearly demonstrated, and research on type 1 diabetes has already contributed greatly to improved management of both forms of the disease. For example, a landmark clinical trial in type 1 diabetes, the Diabetes Control and Complications Trial (DCCT), proved that intensive glucose control can prevent or delay damage to the small blood vessels in the eyes, kidneys, and nerves (microvascular complications). The findings of this trial paved the way to studies that replicated these impressive results in patients with type 2 diabetes. Most recently, the DCCT findings were extended to show that intensive control reduces heart attacks and strokes (macrovascular complications), the major cause of death in both forms of diabetes. Because of this pioneering research in type 1 diabetes, close control of blood glucose levels is now a cornerstone of the medical management of both forms of the disease. Moreover, this landmark trial in type 1 diabetes also established the value of hemoglobin A1c (HbA1c) levels—a measurement of blood glucose levels over time—as an outcome measure for future clinical trials in both type 1 and type 2 diabetes, dramatically shortening the cost and duration of clinical trials of new therapies and encouraging development of new therapies for diabetes. The use of HbA1c as an outcome measure was the basis for Food and Drug Administration (FDA) approval of improved forms of injected insulin, inhaled insulin, and several new classes of oral drugs for type 2 diabetes, which when used in combination can delay the need for insulin therapy.

Unfortunately, most national data on the incidence, prevalence, and burden of diabetes do not distinguish between type 1 and type 2 diabetes—although ongoing studies may help to address this problem. Within the context of available data, it is generally estimated that type 1 diabetes accounts for 5 to 10 percent of all diagnosed cases of diabetes in the U.S. (5). However, the burden of type 1 diabetes is disproportionate to its prevalence because complications and loss of quality life years are much greater when diabetes strikes at younger ages. Collectively, both type 1 and type 2 diabetes constitute an enormous public health challenge in the United States. Although this Strategic Plan is focused on type 1 diabetes, the following indicators of the overall burden of diabetes are presented because the best available epidemiological data are reported for diabetes as a whole.

- Patients with diabetes have an increased risk of heart disease and heart attacks, stroke, high blood pressure, kidney failure, blindness, nerve pain and other neurological problems, limb amputation, chronic wounds and skin ulcers, periodontal disease, depression, and pregnancy-related problems.
- In the past 25 years, the number of people with diabetes has more than doubled to 20.8 million (5, 6), or 7 percent of the total U.S. population (5). Evidence now suggests that one in three Americans born in 2000 will develop diabetes during his or her lifetime (6). It is generally believed that these trends are largely attributable to type 2 diabetes, and related to increases in obesity, a known risk factor for type 2 diabetes, as well as to changes in demographics, such as increases in the elderly and minority populations of the United States who are prone to developing type 2 diabetes. Rates of type 1 diabetes are increasing in some European countries where reliable data is available. More

1944



Standard insulin syringe is developed, helping to make diabetes management more uniform.

1948

Development of delayed action insulin reduced the number of daily insulin injections.

1950

National Institute of Diabetes & Digestive & Kidney Diseases

Medical Research Act established national research institute for diabetes, which later became NIDDK.

1950

Discovery that insulin promotes glucose transport.

1955

Amino acid sequence of insulin protein determined.

limited data suggests that rates of type 1 diabetes are increasing in very young children and infants in the U.S. Baseline national data on diabetes in children has recently been collected in the U.S., and the next phase of this study will provide definitive information on whether type 1 diabetes rates in children are stable or changing.

- Diabetes is the sixth leading cause of death in the United States, resulting in more than 73,000 deaths in 2002 (7). More than 224,000 people die annually from diabetes-related complications common to both type 1 and type 2 diabetes. This number is considered to be significantly underreported (5).
- The problem of diabetes extends globally. The World Health Organization estimated that 1,125,000 people worldwide would die from diabetes in 2005 (8). Overall, the risk of death for individuals with diabetes is approximately double that of people without diabetes of similar age (5).

The burden of both forms of diabetes extends far beyond mortality. In the United States each year, 12,000 to 24,000 people become blind as a result of diabetic eye disease and approximately 82,000 people undergo diabetes-related amputations (5). Encouragingly, declines in the incidence of end-stage renal disease (ESRD) due to diabetes are being noted for the U.S. population, in reports from the United States Renal Data System. These improvements are most noteworthy in patients under age 30 with diabetes (most of whom have type 1 diabetes) and have been observed in Caucasians, but not in African Americans (9). However, ESRD remains a major public health problem. In 2003, 45,330 Americans with diabetes began treatment for irreversible kidney failure (ESRD), and 165,113 people with failed kidneys needed chronic dialysis or a kidney transplant to remain alive (9).

The financial burden of diabetes is tremendous. The direct and indirect costs associated with both forms of diabetes in the United States during 2002 were estimated to be $132 billion (5). The average annual health care costs for a person with diabetes are $13,243, which is 2.4 times greater than those for an individual without diabetes (10). In 2002, 11 percent of national health care expenditures were directed to diabetes care (10). The costs of treating the complications of diabetes, which both forms of the disease share in common, account for much of the health care costs associated with the disease. Although estimates of the rates of diabetes have increased since 2002, the associated cost estimates have not yet been revised; hence, the economic data given here are conservative. Clearly, the economic and societal burden of diabetes has a profound impact on the Nation.

Incidence and Prevalence of Type 1 Diabetes

In the United States, it is estimated that approximately 1 in every 400 to 600 children and adolescents has type 1 diabetes (5). There is evidence that the incidence (the number of new cases) and prevalence (the total number of cases) of the disease are increasing in Europe. In the United States, the incidence and prevalence of type 1 diabetes are not precisely known because of the lack of uniform national data on the rates of childhood diabetes and how the rates are changing over time. This gap in knowledge is being addressed by the Search for Diabetes in Youth Study (SEARCH), which is determining the prevalence and incidence of diabetes in children and youth less than 20 years of age. Emerging data from the SEARCH study (11) suggests that the incidence of type 1 diabetes in American children may be higher than an earlier estimate of 13,000 per year (12). In total, about 30,000 people (children and adults) are diagnosed with type 1 diabetes annually (12).

Key Features of Type 1 Diabetes

Type 1 diabetes is an autoimmune disease in which the body's own immune system attacks and destroys specialized cells of the pancreas called beta cells. Beta cells are found within tiny clusters called islets and produce the hormone insulin. Insulin is required for survival; it sends signals to the body's cells and tissues, telling them to absorb glucose to use as a fuel. Without this vital hormone, the cells and tissues do not absorb glucose and patients can starve to death, despite having high levels of glucose in their bloodstream. An interplay of

1956

Development of the "dip-and-read" urine test allowed instant monitoring of glucose levels.

1959

Immunoassay allowed researchers to measure insulin in blood. This assay showed that patients with type 1 diabetes produced no insulin, but patients early in the course of type 2 diabetes had more insulin than normal.

1960

Self-monitoring of blood sugar with the "wet" method using glucose oxidase strips.

1964

First kidney transplants in patients with diabetes.

1966

First successful pancreas transplant performed.

genetic and environmental factors is responsible for the onset of type 1 diabetes (as well as type 2 diabetes). Having a family member with the disease puts one at higher risk for developing type 1 diabetes.

Type 1 diabetes differs from type 2 diabetes—which is more commonly diagnosed in adulthood, is strongly associated with overweight and obesity, and disproportionately affects minority populations. Although patients with type 1 diabetes require externally administered insulin to survive, type 2 diabetes patients may be treated with medications that make their tissues more sensitive to insulin or enhance insulin production or, in some cases, may be treated with insulin itself.

Treatment Options and Challenges

The treatment of patients with type 1 diabetes was revolutionized in 1921 with the discovery of insulin by a group of researchers at the University of Toronto. To this day, insulin therapy continues to save the lives of patients with type 1 diabetes by replacing the essential hormone that their bodies no longer adequately produce. However, insulin therapy, whether through injections or via a pump, is not a cure and it cannot prevent complications. To manage the disease, patients must carefully monitor their food intake and physical activity. They must perform painful finger sticks multiple times a day to draw blood and test their glucose levels. Based on this monitoring, patients often give themselves several shots of insulin a day, or calculate the correct amount of insulin to administer through their insulin delivery pumps. This regimen is not just "once in a while;" it is every day of their lives. As many patients and their parents say: "There is never a day off from diabetes." Moreover, no matter how vigilant patients are at regulating their blood glucose levels, they can never achieve the fine-tuned regulation provided by a healthy pancreas, which exquisitely senses and responds to insulin needs with precise timing.

Because of the inadequacies of insulin treatment, patients with type 1 diabetes are susceptible to harmful fluctuations in their blood glucose levels—abnormally high blood glucose (hyperglycemia) or dangerously low blood glucose (hypoglycemia). Both of these conditions can be life threatening in extreme cases. In the case of a very young type 1 diabetes patient who cannot self-monitor, parents must assume the role that is no longer performed by the pancreas. The psychosocial impact on families is enormous. Parents often forego restful sleep because they are "on watch" to ensure that their child's blood glucose levels do not fall dangerously low in the middle of the night. They are also dependent on an extended team of caregivers when their child is not in their immediate care, such as school personnel, childcare providers, friends, and parents of their child's friends.

Approaches for Preventing or Reversing the Disease

Currently, there are no known methods to prevent type 1 diabetes. However, recent clinical trials suggest that it may be possible to reverse or slow the rate of loss of the insulin-producing beta cells in newly diagnosed patients. While the environmental factors that may play a role in triggering type 1 diabetes remain to be defined, several key genes that increase the risk of type 1 diabetes have been identified. Genetic tests in combination with blood tests to detect antibodies directed against the insulin-producing beta cells can predict development of type 1 diabetes, allowing new strategies for prevention to be tested. Key strategies for preventing much of the burden of the disease include early detection, improved methods and delivery of care, and new interventions.

With the number of individuals with diabetes increasing, the associated societal and economic burdens will continue to rise. Yet, there are many positive developments, including reports showing that life expectancy for patients with type 1 diabetes is increasing (13). A key finding of NIH-supported research is that intensive control of blood glucose levels can dramatically prevent or delay the development of disease complications. Now, it is essential to find more effective ways to achieve blood glucose control. Progress being made in

1967

Laser treatment revolutionized the care of diabetic retinopathy.

1969

Determination of the three-dimensional protein structure of insulin.

1971

NIH scientists discover the insulin receptor: a protein on the cell surface that mediates effects of insulin in cells.

1974

Evidence that type 1 diabetes is an autoimmune disease provided by discovery of antibodies to insulin-producing cells in newly diagnosed patients and by genetic studies showing the association of type 1 diabetes with the HLA genes that control the immune system.

1977

Introduction of insulin pumps for continuous delivery of insulin.

the area of cell-based research could lead to ways to replace or restore a patient's insulin-producing capacity. Increased knowledge about the underlying mechanisms of beta cell development and function could potentially be used to develop therapeutic approaches to reverse the disease by promoting formation of new beta cells in the pancreas.

With continued, vigorous research, new strategies may be developed to prevent type 1 diabetes in those at risk, restore insulin independence in patients already diagnosed, and prevent the development of disease complications. Through research in these and other avenues, the burden of type 1 diabetes on people and the Nation can be lifted.

GOALS OF TYPE 1 DIABETES RESEARCH

The promise of a cure for type 1 diabetes can only be realized through the vigorous support of scientific research. Type 1 diabetes research supported by the NIH is focused around six overarching research Goals listed below. Pursuit of research toward attaining each of these broad, scientific Goals can help achieve real progress in the understanding, prevention, treatment, and cure of type 1 diabetes and its complications. The Goals are interdependent in that research on one Goal will inform research on others. Therefore, to maximize research progress, research toward achieving the Goals requires well-coordinated and integrated efforts, as described in this Strategic Plan.

Six Overarching Goals of NIH-Supported Type 1 Diabetes Research

- **Goal I: Identify the Genetic and Environmental Causes of Type 1 Diabetes**
- **Goal II: Prevent or Reverse Type 1 Diabetes**
- **Goal III: Develop Cell Replacement Therapy**
- **Goal IV: Prevent or Reduce Hypoglycemia in Type 1 Diabetes**
- **Goal V: Prevent or Reduce the Complications of Type 1 Diabetes**
- **Goal VI: Attract New Talent and Apply New Technologies to Research on Type 1 Diabetes**

Goal I: Identify the Genetic and Environmental Causes of Type 1 Diabetes

Type 1 diabetes has a strong genetic basis that is modified by environmental factors. It is a "polygenic" disease, which means that it arises from the interaction of variations in multiple genes. Research has already identified some genes that are important in the development of type 1 diabetes. However, researchers have not yet found all of the genes that can play a role in disease development. Identification of key genes will not only help to predict who will develop the disease, but will also aid in the development of new prevention strategies. In addition to genes, the environment has also been found to play an important role in the development of type 1 diabetes. Potential environmental triggers are thought to include viruses, dietary factors, environmental toxins, and psychological stress. To date, no single trigger has been conclusively identified. Research to identify the key environmental trigger(s) could be used to prevent the disease in genetically susceptible people.

Goal II: Prevent or Reverse Type 1 Diabetes

One obvious way to attack type 1 diabetes is to stop it before it starts. Preventing the disease means that patients would not require insulin administration or develop life-threatening disease complications. While recent clinical trials have suggested that further loss of insulin production can be slowed

1978

Development of glycosylated hemoglobin (HbA1c) test permitted monitoring average blood glucose control over a 90-day period.

1978

Insulin gene becomes first human therapeutic protein to be cloned and synthesized by genetic engineering.

1980

Development of first animal model of type 1 diabetes that could be used to test drugs for type 1 diabetes: non-obese diabetic (NOD) mouse.

1983

Introduction of the first biosynthetic human insulin.

1983

Clinical studies showed that preconception care of women with diabetes dramatically reduced congenital malformations in their babies.

in patients with newly diagnosed type 1 diabetes, research has not yet identified an effective disease prevention strategy. However, the ability to identify at-risk individuals permits promising strategies for prevention to be tested in rigorously designed clinical trials. Further research and increasing knowledge about what goes wrong with the immune system will facilitate the discovery of novel ways to prevent autoimmunity, and thus prevent disease onset.

In addition to preventing the disease before beta cell destruction starts, it is important to conduct research to prevent further beta cell destruction in newly diagnosed patients. Research has shown that, after patients are diagnosed with the disease, they still have some beta cell function and can produce C-peptide, a by-product of insulin production which is co-secreted from the beta cell with insulin and is a useful measure of endogenous insulin production. Furthermore, clinical studies have demonstrated major benefits of residual beta cell function in patients with type 1 diabetes, even though the patients require insulin therapy. For example, the DCCT demonstrated that higher and sustained levels of C-peptide were associated with reduced incidence of long-term disease complications of the kidneys and the eyes, as well as reduced hypoglycemia. This evidence suggests that preserving patients' remaining beta cell function could have dramatic, long-term health benefits. Already one agent has been shown to preserve beta cell function in new onset type 1 diabetes. To prevent or reverse beta cell destruction in newly diagnosed patients, further research efforts are required to identify and test additional strategies that may provide more durable benefits and few side effects.

Goal III: Develop Cell Replacement Therapy

Patients with type 1 diabetes require insulin therapy because their immune systems have destroyed their pancreatic beta cells. A real "cure" for this disease could be achieved by replacing those missing cells, and scientists are aggressively pursuing this avenue of research. A major breakthrough occurred in 2000 when researchers at the University of Alberta in Edmonton, Canada, reported that patients with type 1 diabetes achieved insulin independence after transplantation with islets from two to four donor pancreata and treatment with a novel immunosuppressive regimen that omitted the widely used glucocorticoid drugs that are toxic to islets. A major barrier limiting the widespread use of islet transplantation is the shortage of islets available for transplantation. The diabetes research community believes that there is significant potential in the use of human embryonic[1] and tissue-specific adult multipotent progenitor cells in deriving a host of differentiated cell types, including insulin-producing beta cells. Understanding the underlying molecular mechanisms of beta cell biology, and how mature beta cells are formed from stem/progenitor cells, could help to overcome this barrier. Furthermore, as noted previously, recent research has shown that patients with type 1 diabetes have some remaining functional beta cells. Therefore, research on the mechanisms controlling islet cell growth and regeneration could lead to novel therapies designed to stimulate beta cell growth *in vivo*.

Another major barrier that prevents islet transplantation from being a widespread treatment option for patients with type 1 diabetes is the need for lifelong immunosuppressive drug treatments that are currently required to prevent rejection of transplanted islets. Research to identify ways to overcome the need for immunosuppressive treatment, or to identify less toxic immunosuppressives, can help to make islet transplantation a reality for greater numbers of patients with type 1 diabetes.

Goal IV: Prevent or Reduce Hypoglycemia in Type 1 Diabetes

Hypoglycemia is perhaps the most distressing acute complication of type 1 diabetes. Hypoglycemia can occur with missed meals, during exercise, or when too much insulin is in the body, which causes glucose to fall to dangerously low levels. Too little glucose means that the body—and particularly the brain—cannot function at its normal capacity. The immediate effects of hypoglycemia can include changes in cardiovascular and nervous system function, cognitive

[1] The NIH supports human embryonic stem cell research consistent with federal funding policies.

1984

Identification of early kidney disease marker—microalbuminuria—permitted doctors to intervene to prevent or delay kidney failure.

1987

Diabetic foot ulcers treated by total contact casting.

1990

First successful transplant of human islet cells reversed insulin dependency in patients.

1993

Diabetes Control and Complications Trial (DCCT) demonstrated that intensive therapy delays the progression of long-term complications of the eyes, kidneys, and nerves.

1993

Collaborative study of diabetic nephropathy showed that ACE inhibitors reduce need for kidney dialysis and transplantation, and cut heart disease mortality.

impairment, increased risk for unintentional injury, coma, and sometimes death. In some cases, patients are not aware that their blood glucose level is dangerously low. This syndrome is called "hypoglycemia unawareness." It is characterized by the loss of the warning symptoms that alert patients that it is time to eat before their blood glucose level falls too low. In addition, episodes of hypoglycemia impair defenses against future hypoglycemia, resulting in a vicious cycle of recurrent episodes.

A severe limitation to the practice of intensive glucose control to prevent disease complications is the potential for acute episodes of hypoglycemia. It is estimated that patients on intensive treatment have two hypoglycemic episodes a week versus one episode if they are treated less intensively (14). Because intensive glucose control dramatically reduces the risk of long-term disease complications, it is imperative to pursue research to overcome this major obstacle to achieving tight glucose control. The risk of severe hypoglycemia may be related to a variety of behavioral and psychological variables, and behavioral interventions may reduce these risks. Strategies to meld technological, behavioral, and educational advances are key to this goal. Devices for minimally invasive continuous glucose monitoring, developed with NIH support and recently approved by the FDA, may represent a major advance in this regard. Further research is needed to improve glucose monitoring, to link monitoring devices to insulin delivery, and to empower patients and care providers to maximize the benefits of these devices. By reducing hypoglycemic episodes, improving glycemic control, and lessening the burdens of diabetes self-management, this research can also have a major impact on patients' quality of life until cell replacement therapy becomes a viable option for patients with type 1 diabetes.

Goal V: Prevent or Reduce the Complications of Type 1 Diabetes

Nearly every organ in the body is adversely affected by type 1 diabetes. Throughout the course of a patient's life, the persistent elevation in blood glucose levels despite insulin therapy damages vital organs, including the heart and kidneys. The longer a person has the disease, the more likely it is that he or she will develop these severe complications. Because patients with type 1 diabetes are often diagnosed in childhood and adolescence, they may develop complications at a young age.

The DCCT reported good news regarding preventing or delaying the onset of complications. Completed in 1993, the trial compared the relationship between intensive versus conventional treatment of blood glucose levels and the development of disease complications. The DCCT proved conclusively that intensive therapy reduces the risk of microvascular complications, such as diabetic eye, kidney, and nerve disease. Nearly all patients who participated in the DCCT volunteered to continue to be followed in the Epidemiology of Diabetes Interventions and Complications Study (EDIC), which began in 1994. The DCCT/EDIC researchers continue to report remarkable long-term benefits of intensive blood glucose control in preventing or delaying complications of the eyes, kidneys, and the heart. However, given the limitations and difficulties of current therapies and technologies for achieving good glucose control, even most participants in the EDIC study cannot achieve the levels of control associated with reduced complications. Thus, other approaches are needed to prevent and delay progression of complications. New insights into the underlying molecular mechanisms of diabetes complications are imperative in order to develop new therapeutic approaches.

Goal VI: Attract New Talent and Apply New Technologies to Research on Type 1 Diabetes

Research on type 1 diabetes spans a broad range of scientific disciplines, including endocrinology and metabolism; immunology; genetics; epidemiology; clinical trials; neuroscience; behavioral science; cell, developmental, and vascular biology; and the physiology of the heart, eyes, kidneys, and urologic tract, and the central and peripheral nervous systems. Propelling research progress on the understanding, prevention, and cure of type 1 diabetes requires a cadre of scientists with

1998	2000	2000	2002	2002	2003
 First year of *Special Statutory Funding Program for Type 1 Diabetes Research.*	"Edmonton" Protocol improved success rate of islet transplantation from less than 5 percent to 90 percent.	Long-term follow-up of patients from DCCT suggested that the benefits of tight glucose control have a sustained effect on diabetes complications, a phenomenon called "metabolic memory."	The Diabetes Prevention Trial-Type 1 (DPT-1) demonstrated the feasibility of accurate assessment of risk for type 1 diabetes.	Research demonstrated that treating new onset type 1 diabetes patients with a monoclonal antibody preserves residual beta cell function.	The rate of kidney failure has stabilized in part due to improved management of diabetes.

diverse research training and expertise. Furthermore, it is critical for basic scientists and clinical researchers to work together to translate research findings from the bench to the bedside, and from the bedside to clinical practice, in order to achieve real improvements in patients' health and quality of life.

Powerful new technologies that have emerged over the past few years make this an exciting time to be involved in scientific research and have quickened the pace of discovery. Application of these new and emerging technologies to type 1 diabetes research provides unprecedented opportunities to solve key problems. For example, "proteomics" involves the use of novel, integrated technologies to identify and quantitate proteins and study their interactions. Identifying how protein expression changes over the course of type 1 diabetes onset and progression can help researchers understand the underlying disease processes, develop biomarkers of disease onset and progression, and propose and test novel prevention and treatment strategies. Type 1 diabetes research stands to benefit greatly from the application of proteomics and many other new and emerging technologies.

NIH TYPE 1 DIABETES RESEARCH PORTFOLIO

The NIH vigorously pursues and supports research on the understanding, prevention, and cure of type 1 diabetes. Current efforts span diverse areas, such as genetics, genomics, proteomics, immunology, developmental biology, imaging, bioengineering, glucose sensing, and insulin delivery. NIH-supported clinical trials are testing promising agents for type 1 diabetes and its complications. Type 1 diabetes research at the NIH is largely supported by regularly appropriated funds that the Department of Health and Human Services (HHS) receives for diabetes research through the Labor-HHS-Education appropriations subcommittees. In addition, it is supported by the *Special Statutory Funding Program for Type 1 Diabetes Research*, which the NIDDK administers on behalf of the Secretary and in collaboration with multiple NIH Institutes and Centers, as well as the CDC.

Critical to the national effort to combat type 1 diabetes are studies funded through investigator-initiated research grants (primarily R01 grants). The NIH vigorously supports investigator-initiated research projects, and also fosters development of research efforts in areas of particular importance and opportunity through solicitations for grant applications and research contract proposals. This type of research has provided remarkable insights about type 1 diabetes and has laid the foundation for the development of improved treatment approaches and possible prevention strategies. Much of the positive impact of NIH-supported research comes from creative, hypothesis-driven endeavors undertaken by outstanding investigators working in laboratories across the country, funded through a peer-reviewed, highly competitive process. In addition, type 1 diabetes research has benefited from the results of other major cross-cutting NIH efforts such as the wealth of genetic information flowing from the Human Genome Project and the expanded knowledge base NIH research has fueled regarding developmental and cell biology, autoimmunity, and transplantation biology.

Complementing and extending this research base, the *Special Funding Program* has furthered the creation of unique, collaborative, and innovative research consortia and clinical trials networks to increase understanding about the prevention, treatment, and cure of type 1 diabetes. Initiatives supported by this program differ in size, scope, duration, and nature from other type 1 diabetes efforts supported through regular NIH appropriations. The *Special Funding Program* enabled the initiation of most of these large-scale, high-impact efforts, at a scientifically optimal scale of operation. Importantly, the research efforts that have been supported to date have

2005

DAISY study found that genetically vulnerable newborns can be identified and followed prospectively to prevent diabetic ketoacidosis, the leading cause of diabetes-related morbidity and mortality in infants.

2005

Long-term follow-up of patients from the DCCT demonstrated that intensive therapy reduces cardiovascular complications.

2006

FDA approved the first inhaled version of insulin.

2006

First generation of FDA-approved continuous glucose monitors paired with insulin pumps pave the way for developing an artificial pancreas and closing the feedback loop between glucose levels and insulin delivery.

spurred numerous future opportunities that could dramatically improve the lives of patients with type 1 diabetes. The following are highlights of some of the major collaborative research efforts and innovative approaches that are supported by the *Special Funding Program*. These research efforts are illustrative examples and not a comprehensive overview of the entire NIH type 1 diabetes research portfolio.

Goal I: Identify the Genetic and Environmental Causes of Type 1 Diabetes

***Search for Diabetes in Youth (SEARCH)*:** There are no comprehensive population-based estimates of diabetes burden among American youth. SEARCH will define the prevalence and incidence of diabetes in children and youth less than 20 years of age in six geographically dispersed populations that encompass the ethnic diversity of the United States. This study will help increase understanding of how type 1 diabetes strikes and unfolds.

***The Environmental Determinants of Diabetes in the Young (TEDDY)*:** The goal of TEDDY is to identify environmental causes of type 1 diabetes in genetically susceptible individuals. This long-term study is enrolling at-risk newborns and then following them until they are 15 years of age. The study is crucial to helping researchers understand the environmental triggers that play a role in type 1 diabetes disease onset and development.

***Type 1 Diabetes Genetics Consortium (T1DGC)*:** T1DGC is organizing international efforts to identify genes that determine an individual's risk of developing type 1 diabetes. This Consortium is currently recruiting 2,800 family members who have two or more siblings with type 1 diabetes in order to identify genes that increase susceptibility. Finding these genes will not only increase understanding of the underlying molecular mechanisms of disease development, but also aid in the discovery of novel prevention strategies and identification of patients who could benefit from these approaches.

Goal II: Prevent or Reverse Type 1 Diabetes

***Cooperative Study Group for Autoimmune Disease Prevention (Prevention Centers)*:** The mission of the Prevention Centers is to engage in scientific discovery that significantly advances knowledge about the prevention and regulation of autoimmune diseases, including type 1 diabetes. Pre-clinical research conducted by the Prevention Centers is key to the development of strategies for modulating the immune system so that they can be tested in human clinical trials.

***Immune Tolerance Network (ITN)*:** Immune tolerance is the process by which the immune system accepts a protein or other molecule as "self" and does not attempt to destroy cells or tissues containing that protein. Tolerance induction can block the autoimmune process underlying type 1 diabetes or enable the body to accept transplanted islets without the need to globally suppress the immune system. Research conducted through the ITN is evaluating new treatments to induce tolerance in type 1 diabetes, as well as other disease areas. The ITN is currently conducting and developing several clinical trials related to type 1 diabetes and islet transplantation. Research on tolerance is critical both for developing therapies to slow or reverse type 1 diabetes, as well as for improved approaches to islet transplantation.

***Standardization Programs*:** Standardized assessment of key measures for type 1 diabetes research is extremely important to ensure consistency across laboratories and clinical trial networks, so that data can be compared and combined. Efforts are ongoing to improve and standardize the measurement of autoantibodies (used to identify initiation of autoimmunity), C-peptide (a measure of beta cell mass and function), and HbA1c (a measure of long-term blood glucose control).

***Trial To Reduce IDDM in the Genetically At Risk (TRIGR)*:** This multicenter, international study is comparing the development of type 1 diabetes in genetically susceptible infants who are weaned onto a hydrolysate of cow's milk formula, in which many of the cow proteins have been broken down, versus standard cow's milk formula. TRIGR, which is currently in the patient recruitment phase, could have a major impact on disease prevention if differences are observed between the two types of formulas.

***Type 1 Diabetes TrialNet (TrialNet)*:** TrialNet is an international network of investigators, clinical centers, and core support facilities. It supports the development and implementation of clinical trials of agents to slow the progression of type 1 diabetes in new onset patients and to prevent the disease in at-risk patients. TrialNet has launched several studies that are recruiting patients and is currently evaluating several other therapeutic agents to test in the network. This type of collaborative network infrastructure is

critical for facilitating clinical trials in type 1 diabetes, as well as for making real improvements in patients' health by identifying new therapeutic agents.

Goal III: Develop Cell Replacement Therapy

***Beta Cell Biology Consortium (BCBC)*:** The mission of this Consortium is to facilitate interdisciplinary approaches that will advance understanding of pancreatic islet cell development and function. The long-term scientific goal is to develop a cell-based therapy to restore normal insulin production and action to diabetic patients. Working toward this goal, the BCBC has created and distributed important reagents that will serve the scientific community at large. Research pursued through the BCBC can ultimately help to overcome a major barrier to islet transplantation—the shortage of islets.

***Clinical Islet Transplantation Consortium (CIT)*:** The purpose of this Consortium is to develop and implement a program of single- and/or multicenter clinical studies, accompanied by mechanistic studies, in islet transplantation with or without accompanying kidney transplantation, for the treatment of type 1 diabetes. Research pursued through this Consortium aims to make improvements in the field of islet transplantation and to share the data and results with the broad scientific community.

***Collaborative Islet Transplant Registry (CITR)*:** The mission of the CITR is to expedite progress and promote safety in islet transplantation through the collection, analysis, and communication of comprehensive, current data on all islet transplants performed in North America. The CITR prepares an annual report with data on recipient and donor characteristics, pancreas procurement and islet processing, immunosuppressive medications, function of the donated islets, patients' lab results, and adverse events. This information will help to define the overall risks and benefits of islet transplantation as a treatment option for patients with type 1 diabetes.

***Immunobiology of Xenotransplantation Cooperative Research Program*:** This multi-institution Program is developing and evaluating pre-clinical porcine to non-human primate models of xenotransplantation (solid organ, tissue, or cell transplantation between species). The Program supports pre-clinical research to address immunological and physiological issues critical to the engraftment, survival, and function of xenografts. The long-term goal is to develop novel and efficacious strategies for broad clinical application of xenotransplantation.

***Islet Cell Resource Centers (ICRs)*:** The ICRs serve as regional centers that provide clinical grade human islets to investigators engaged in islet transplantation protocols throughout the country; optimize the procedures used to obtain such islets; and distribute human pancreatic islets to investigators for use in laboratory-based research studies. This resource provides high-quality islets for use in human islet transplantation research and allows researchers to continue to investigate islets in basic research studies.

***Non-human Primate Transplantation Tolerance Cooperative Study Group (NHPCSG)*:** This multi-institution Study Group was established to evaluate the safety and efficacy of novel therapies to induce immune tolerance in non-human primate models of kidney and islet transplantation. The Group also supports research on immune tolerance. Pre-clinical research conducted by this Group will help scientists move promising therapeutic agents from the laboratory into human clinical trials.

Goal IV: Prevent or Reduce Hypoglycemia in Type 1 Diabetes

***Diabetes Research in Children Network (DirecNet)*:** The focus of DirecNet is to investigate the use of technological advances in the management of type 1 diabetes in children and to develop a better understanding of hypoglycemia. The Network's goals include assessing the accuracy, efficacy, and effectiveness of continuous glucose monitoring in children with type 1 diabetes, and determining the extent to which exercise contributes to the risk of hypoglycemia. Until cell replacement therapy is a viable treatment option for children with type 1 diabetes, research on glucose sensing and insulin delivery is crucial to improving quality of life and decreasing the number of hypoglycemic episodes.

Goal V: Prevent or Reduce the Complications of Type 1 Diabetes

***Animal Models of Diabetic Complications Consortium (AMDCC)*:** The AMDCC is an interdisciplinary Consortium designed to develop animal models that closely mimic the human complications of diabetes for the purpose of studying disease pathogenesis, prevention, and treatment. The Consortium has already developed a number of

promising models for complications involving the heart, kidneys, and nervous system. Development of animal models is essential for pre-clinical drug development.

***Diabetic Retinopathy Clinical Research Network (DRCR.net)*:** Type 1 diabetes causes damage to the eyes and may lead to blindness. The DRCR.net conducts multicenter clinical research studies to test promising therapeutic agents for the treatment of two forms of diabetic eye disease—diabetic retinopathy and diabetic macular edema—and associated conditions. Because blindness is such a severe and debilitating disease complication, research pursued through this network could dramatically improve patients' quality of life.

***Epidemiology of Diabetes Interventions and Complications Study (EDIC)*:** The aim of EDIC is to study the clinical course and risk factors associated with the long-term complications of type 1 diabetes, using the cohort of the DCCT. The DCCT/EDIC research group has observed dramatic long-term benefits of intensive glucose control in preventing and delaying complications of the eyes, kidneys, nerves, and heart. These results have had a major impact on the clinical care of diabetes patients.

***Family Investigation of Nephropathy and Diabetes (FIND)*:** The FIND Consortium is carrying out studies to elucidate the genetic susceptibility to kidney disease in patients with diabetes, as well as genetic susceptibility to retinopathy in diabetic patients. A family-based study recruited more than 2,500 affected and discordant pairs of siblings. A separate case control study is completing recruitment of more than 3,000 individuals. These studies will help researchers understand the genetic underpinnings of the kidney and eye complications of diabetes, which can, in turn, inform prevention and treatment strategies.

***Genetics of Kidneys in Diabetes Study (GoKinD)*:** GoKinD was established to study the genetics of kidney disease in patients with type 1 diabetes. The study group has collected and is distributing DNA and other biological samples from more than 1,700 adults with type 1 diabetes in the United States and Canada. Scientists will use these samples to identify genes that are important in the development of, or resistance to, diabetic kidney disease.

Goal VI: Attract New Talent and Apply New Technologies to Research on Type 1 Diabetes

***Research Training and Career Development in Pediatric Diabetes*:** This program provides support of research training and career development in pediatric diabetes at institutions that have environments, mentors, and programs that will make them particularly effective in enhancing the number of independent investigators contributing to research in pediatric diabetes. The awards, through the T32 (institutional research training) and K12 (clinical scientist career development program) grant mechanisms of the NIH, are intended to provide an opportunity for continuous training from the clinical fellowship years to emergence as a fully trained independent investigator. These integrated programs are designed to prepare pediatricians, selected by the institution, for careers in pediatric endocrinology research related to diabetes.

***Type 1 Diabetes—Rapid Access to Intervention Development (T1D-RAID)*:** The T1D-RAID program provides resources for manufacture and pre-clinical development of drugs, natural products, and biologics that will be tested in type 1 diabetes clinical trials. The goal of T1D-RAID is to facilitate the translation of promising therapeutic agents from the bench to the bedside, in order to more rapidly impact patients' health.

> For more information on these and other type 1 diabetes research efforts, please visit a Web site dedicated to research supported by the *Special Statutory Funding Program for Type 1 Diabetes Research*: www.T1Diabetes.nih.gov.

Collaborative Planning Process

The NIDDK is the lead Institute at the NIH for pursuing type 1 diabetes research. Because this research involves diverse scientific disciplines, the NIDDK collaborates extensively with other NIH Institutes and Centers, as well as other government agencies. Type 1 diabetes research involves nearly every Institute and Center of the NIH, including the National Center for Research Resources (NCRR), National Eye Institute (NEI), National Human Genome Research Institute

(NHGRI), National Heart, Lung, and Blood Institute (NHLBI), National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Biomedical Imaging and Bioengineering (NIBIB), National Institute of Child Health and Human Development (NICHD), National Institute of Dental and Craniofacial Research (NIDCR), National Institute of Environmental Health Sciences (NIEHS), National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Nursing Research (NINR), National Library of Medicine (NLM), and other NIH Institutes and Centers that are represented on the statutory Diabetes Mellitus Interagency Coordinating Committee (DMICC). The NIH also works closely with the CDC, the FDA, the Centers for Medicare & Medicaid Services (CMS), and other governmental agencies represented on the DMICC. Also contributing to program planning are the two major diabetes voluntary organizations, the Juvenile Diabetes Research Foundation International (JDRF) and the American Diabetes Association (ADA).

DEVELOPMENT OF THE STRATEGIC PLAN

Origin and Purpose of the Plan

In January 2005, the NIDDK convened an *ad hoc* planning and evaluation meeting of external scientific and lay experts in type 1 diabetes. The purpose of the meeting was to perform a mid-course assessment of many currently funded type 1 diabetes research programs, and to identify future research opportunities within this context. The meeting focused on research consortia and clinical trials networks supported by the *Special Statutory Funding Program for Type 1 Diabetes Research*. A detailed summary of the meeting can be accessed on the NIDDK Web site at: www.niddk.nih.gov/federal/planning/Jan-18-19-T1D-FINAL.pdf.

One of the recommendations emanating from this meeting was to initiate a much broader review of the entire state-of-the-science with respect to type 1 diabetes, including recent research advances and emerging opportunities. Such a review would be far more encompassing and future-oriented than the assessment performed at the January 2005 meeting, which was largely focused on existing programs. In response to this recommendation, the NIDDK Director announced in March 2005, that the Institute would spearhead a new strategic planning effort in type 1 diabetes research under the auspices of the statutory DMICC, chaired by the NIDDK. The membership of this Committee includes all NIH components involved in diabetes research, as well as other relevant Federal agencies.

The purpose of this Strategic Plan is to serve as a scientific guidepost to the NIH and to the investigative and lay communities by identifying compelling research opportunities. These scientific opportunities will inform the priority-setting process for the type 1 diabetes research field and propel research progress on the understanding, prevention, treatment, and cure of type 1 diabetes and its complications.

Collaborative Planning Process

The Strategic Plan was developed with broad input from a diverse and talented group of researchers and lay experts dedicated to advancing type 1 diabetes research (please see Appendix A). Participants included representatives from the NIH and other Federal agencies represented on the DMICC, scientists external to the NIH, lay people representing patients' interests, and representatives from diabetes voluntary organizations.

The Strategic Plan was organized around the six overarching goals of type 1 diabetes research. To formulate the Plan, Working Groups were convened to address each of the first five goals. The sixth goal, "Attract New Talent and Apply New Technologies to Research on Type 1 Diabetes," is an overarching goal that is relevant to all of type 1 diabetes research. Therefore, this goal was addressed by each of the five Working Groups. Each Working Group was chaired by a scientist external to the NIH and was composed of other external scientific experts, a lay representative, a representative of a diabetes voluntary organization, at least one member of the DMICC, and other senior scientific Government representatives. The Working Group members were asked to survey the state-of-the-science and develop a summary of progress and opportunities relevant to each goal.

In addition to the Working Groups, the Strategic Plan was informed by insights provided by an overarching Executive Committee, composed of the chairs of the five Working Groups and representatives from the government and from

diabetes voluntary organizations. The Executive Committee met on September 28, 2005, to ensure that in aggregate the components developed by the Working Groups were comprehensive and addressed the most compelling opportunities for the prevention, therapy, and cure of type 1 diabetes and its complications. The Executive Committee provided guidance on integrating the products of each Working Group into a final Strategic Plan that will serve the purpose of informing future priority-setting in type 1 diabetes research.

To solicit broad public input into the strategic planning process, a draft document was posted on the Strategic Plan's Web site (accessed at: www.T1Diabetes.nih.gov/plan) for a month-long period of public comment. Scientists with expertise relevant to type 1 diabetes and its complications and members of voluntary and professional health advocacy organizations were invited to comment. A broad range of expertise was represented among the individuals and organizations providing vigorous input on the draft Strategic Plan.

Organization of the Strategic Plan

Based on the same general content, two versions of this Plan have been developed for: (1) patients with type 1 diabetes, their family members, and the public, and (2) the scientific research community. Both versions contain a summary of major research objectives.

The version of the Plan for patients and the public describes how achieving the goals will directly benefit the health and quality of life of patients with type 1 diabetes and their family members. Each Goal includes the following sections:

- *Why the Goal Is Important:* This section highlights the clinical relevance of the goal and describes how research progress can have a direct and dramatic impact on the lives of patients with type 1 diabetes and their family members.
- *Profiles of Patients or Scientists:* This section describes the impact of type 1 diabetes on the lives of patients with type 1 diabetes and family members, or the experiences of researchers studying the disease.

The technical version of the Plan provides greater detail regarding specific research directions that can be pursued to achieve the overarching goals of type 1 diabetes research. Under each Goal, the following sections are included:

- *Introduction and Background:* A brief description of the current state-of-the-science, and an overview of the importance of the goal in propelling research progress in type 1 diabetes.
- *Recent Scientific Advances:* Examples of major achievements in type 1 diabetes research that have made a significant impact on the research field or patients' health, particularly in the last 5 to 7 years.
- *Research Objectives and Strategies To Achieve Goals:* The objectives are specific research directions that can be pursued to realize the goal of the chapter. The objectives were identified by Working Group members as being critically important for overcoming current barriers and achieving progress in type 1 diabetes research relative to the chapter's overarching goal over the next 10 years. This section also describes some immediate steps that can be taken to achieve the research objectives.

Implementation of the Strategic Plan

Successful implementation of the research objectives outlined in this Strategic Plan requires the collaboration of the multiple Institutes and Centers of the NIH, other government agencies represented on the DMICC, industry, and the diabetes research and voluntary communities. It is only through the involvement and collaboration of these different entities that research progress will be realized.

Although this document, which reflects current research advances and objectives, is necessarily "static," the strategic planning process is dynamic. Novel findings and new technologies can dramatically and positively change the course of planned research. Therefore, to be successful, this Strategic Plan must be periodically assessed by scientific experts in the type 1 diabetes research field, so that new and emerging opportunities can be identified. The DMICC will continue to serve an important role by assessing progress toward attaining the goals and objectives described in this Strategic Plan. The NIH will also continue to solicit input from the external scientific community through forums such as scientific workshops, conferences, and planning and evaluation meetings. This input will continue to be a valuable and necessary component of the NIH's strategic planning process for type 1 diabetes research.

LOOKING FORWARD: FUTURE TYPE 1 DIABETES RESEARCH

Research efforts over the past several decades have led to tremendous improvements in the health and quality of life of patients with type 1 diabetes. The prognosis for newly diagnosed patients has dramatically improved compared to just a decade ago. While these improvements are positive, one thing remains certain: we are not there yet. People with type 1 diabetes still check their blood glucose levels, administer insulin, and develop life-threatening complications. It is imperative to build upon the strong existing research base to not only improve current treatment strategies, but also identify ways to prevent and cure the disease. Because of new and emerging technologies in areas such as genomics, imaging, and systems biology, there is great potential to make significant and dramatic improvements in the health of patients with type 1 diabetes in the near future. Thus, it is important to harness these technologies for type 1 diabetes research and to sustain and intensify the momentum that currently exists in the field. Achieving the specific objectives and making progress toward the overarching research goals outlined in this Strategic Plan will have an enormous impact on patients with type 1 diabetes, as well as on patients with other forms of diabetes and other autoimmune diseases.

Figure Legend: Type 1 diabetes results from an interplay of genetic and environmental factors. A newborn (teal shading) with either a parent or sibling (blue shading) with type 1 diabetes has a greater chance of developing the disease than does a child with no family history. The Environmental Determinants of Diabetes in the Young (TEDDY) study will be following genetically at-risk infants through adolescence to try to identify environmental factors that may trigger disease onset. *(Image modified from figure courtesy of Dr. Marian Rewers and the Diabetes Autoimmunity Study in the Young [DAISY].)*

GOAL I:

IDENTIFY THE GENETIC AND ENVIRONMENTAL CAUSES OF TYPE 1 DIABETES

Why It Is Important To Find The Genetic and Environmental Causes of Type 1 Diabetes

- Unraveling the Complexities of Type 1 Diabetes
- Finding Culprit Genes and Their Role in Autoimmunity
- Consortia for Pooling of Genetic Resources and Talent
- Pursuit of Candidate Genes and Insights from Animal Models
- Environmental Factors
- Long-Term Studies
- Future Implications of This Research

Patient Profile

- Katie and Ellie Clark: Mother and Daughter Living with Type 1 Diabetes

WHY IT IS IMPORTANT TO IDENTIFY THE GENETIC AND ENVIRONMENTAL CAUSES OF TYPE 1 DIABETES

Type 1 diabetes is an insidious, destructive, and costly disease that can strike anyone. Those who don't have the disease usually know someone who does—a family member, friend, neighbor, or coworker. They ask themselves: "Am I also at risk for this disease, can I be tested for it, and how can I prevent it from striking me or my child? Are there any changes I could make to prevent the disease in my family?" Patients living with type 1 diabetes ask: "How did I get this disease? Do I have a bad form of the disease? Will my children or my grandchildren be likely to get it too?"

Unraveling the Complexities of Type 1 Diabetes

In type 1 diabetes, an interplay of genetic and environmental factors is at the root of the immune system's misguided attack on the body's insulin-producing cells (beta cells found in clusters within the pancreas called "islets"). Until these factors are completely deciphered, it will not be possible to know with certainty all those who are at risk for the disease and their specific risk profiles. This knowledge is urgently needed to develop and tailor the most effective clinical strategies for completely preventing the disease. This knowledge would also facilitate research aimed at reversing the disease as soon as possible after its onset—before complications take hold of the eyes, kidneys, nerves, heart, and other parts of the body.

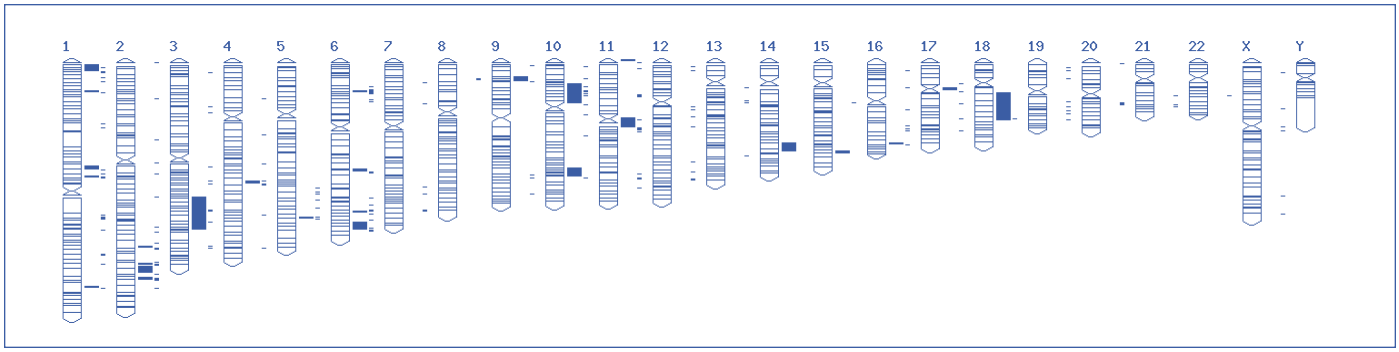
Type 1 diabetes is an extremely complex disease, believed to involve many genes that work in concert and can have both large and small effects. If altered from their healthy state, the genes can cause a person to have a predisposition for the disease. When this genetic susceptibility is "triggered" by an environmental agent, the body's immune defense system will then turn against itself. Ironically, when provoked, the normally protective immune system—which fights against bacteria, viruses, and other foreign invaders—will launch an assault on the body's own insulin-producing cells. This immune system attack on "self" makes type 1 diabetes an "autoimmune" disease.

Finding Culprit Genes and Their Role in Autoimmunity

It is important to find out why some individuals develop type 1 diabetes, while others do not. The likelihood that a person will develop the disease is known to be higher the more closely related he or she is to someone who has type 1 diabetes. However, 80 percent of new patients with type 1 diabetes do not have close relatives with the disease (15). Moreover, even in identical twins, who have the same genetic makeup, it is possible for the disease to affect one, but not the other.

Many research advances have been achieved in the search for "culprit" genes, their variations, and their influence on the immune system. Strong evidence points to four genetic regions that contain suspect genes. However, both laboratory and clinical studies indicate that as many as 20 other regions may contain genes that influence disease susceptibility, and some of these genes may influence it only in certain populations. Moreover, it is possible that greater risk is conferred by specific gene combinations and gene-gene interactions, whereas smaller risk may accompany the presence and interplay of other genes. Teasing apart these differences is extremely difficult.

Research indicates that one of the implicated genetic regions (the major histocompatibility complex or "MHC") may contribute up to 50 percent of the total genetic risk for type 1 diabetes. Moreover, the protein products of genes in this region are of central importance to the body's immune response. It is possible that these gene products affect key immune system cells (T cells) leading them into attacking proteins in the pancreas as if they were invading bacteria or viruses. Other studies have confirmed that some people have a version of the insulin gene that makes them more susceptible to type 1 diabetes. In particular, they have shown that the degree of disease susceptibility is likely to be directly



Human genome map. The lines or bars along the sides of each chromosome represent genetic regions that have been linked to type 1 diabetes.

(Image from Smink LJ, et al. T1DBase, a community web-based resource for type 1 diabetes research. Nucleic Acids Res. Jan 1; 33 Database Issue: D544-D549. 2005.)

influenced by the number of repeated elements in a region of this gene that regulates its expression. Still other research has revealed genes that dampen or eliminate proteins that protect the body against an aberrant immune response.

Consortia for Pooling of Genetic Resources and Talent

Type 1 diabetes research benefits greatly from generic, large-scale projects, such as the Human Genome Project, which have accelerated the study of genes and their function in health and disease. These types of broad efforts provide a knowledge base that can be greatly amplified by the addition of disease-specific genetic data, such as that being garnered by the ongoing NIH-funded international Type 1 Diabetes Genetics Consortium (T1DGC). The Consortium is collecting biosamples from 2,800 families in which two siblings have type 1 diabetes. This resource provides a powerful tool for unraveling the complex underpinnings of the disease, which will be interrogated through the combined expertise of many investigators. Analyses of large study groups offer the statistical power needed to identify and confirm genetic and environmental contributors to complex diseases. Such pooled resources increase the probability of not only defining genetic risk, but also identifying targets toward which new preventive strategies can be directed.

Pursuit of Candidate Genes and Insights from Animal Models

To narrow the gene hunt, researchers have identified and are continuing to focus their efforts on genes believed to be likely "candidates" for contributing to disease onset. Many additional candidate genes will be identified by general immunology studies, research on insulin-producing cells, and investigations of animal models that mirror type 1 diabetes in humans. Discovery of diabetes-causing genes in animal models will propel research on corresponding genes in human tissue samples, and will thus help to uncover the pathways in which the genes function. Every "culprit" gene and pathway that is identified represents a potential target for heading off the disease before its onslaught, or for intervening in the disease before it progresses to serious complications.

Environmental Factors

In parallel with the search for disease-causing genetic factors, it is imperative to uncover the environmental triggers that spark type 1 diabetes. Many people may have a genetic susceptibility to the disease, but may never actually develop it unless something in the environment initiates that genetic machinery. Environmental triggers remain elusive—although research suggests that viruses, diet, environmental toxins, and stress may be implicated. Observed patterns of disease outbreak, as well as seasonality of onset, lend support to the possibility that an infectious agent may act as a trigger. If a viral trigger is revealed, then a vaccine could possibly be developed to prevent disease onset in genetically susceptible individuals. Studies have also suggested that dietary factors, such as vitamins B and D, as well as certain fatty acids, may have protective effects, but more research is needed on the role of these and other dietary factors in disease development.

Importantly, the studies of environmental factors that play a role in type 1 diabetes may also contribute to understanding the development of other autoimmune diseases, such as celiac disease, which primarily affects the gastrointestinal tract. In the United States, the prevalence of celiac disease has been estimated to be approximately one percent (16). Some genes

confer susceptibility to both celiac disease and type 1 diabetes, and many people have both diseases. Therefore, ongoing studies to identify environmental triggers of type 1 diabetes are also investigating development of celiac disease. These studies may uncover environmental factors initiating both disorders, benefiting not only patients with type 1 diabetes, but also people suffering from celiac disease.

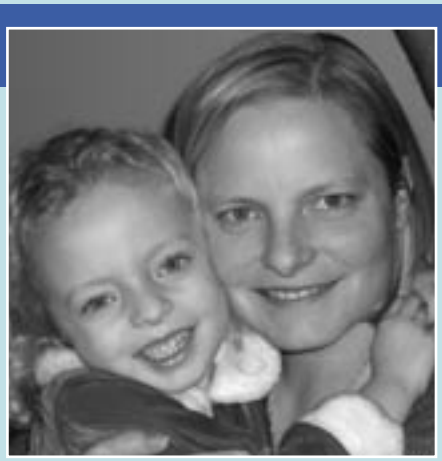
Long-Term Studies

Very long-term studies are required to understand the causes and natural history of type 1 diabetes. Such lengthy studies are needed because environmental triggers of disease may occur in infancy and early childhood, but the disease's onset may be later in childhood, adolescence, or early adulthood. Important efforts to this end are already under way in NIH-funded consortia and should be continued. Recently, scientists directing six independent studies of environmental triggers of type 1 diabetes in the United States and high-risk areas of Europe joined forces to create a united study (The Environmental Determinants of Diabetes in the Young [TEDDY]) with much greater power to uncover potential environmental triggers. Samples from the TEDDY study will be made widely available to researchers worldwide. Already, elimination of early exposure to one potential dietary trigger of type 1 diabetes, cow's milk-based infant formula, is being tested in a clinical trial (Trial to Reduce IDDM in the Genetically at Risk [TRIGR]). While costly, such long-term studies could answer critically important questions about disease risk and onset. The payoff for this substantial investment could be huge—such as a vaccine against an infectious trigger, or dietary change that might protect against development of type 1 diabetes.

Future Implications of This Research

With new insights into the interplay of genetic-environmental factors and immune mechanisms in type 1 diabetes, researchers may be able to identify with great precision those individuals at risk for the disease, and to develop and test prevention-oriented strategies. It is possible, for example, that such new knowledge could point the way toward the screening of newborns, and to even more widespread screening to identify individuals at risk in the general population. This knowledge would facilitate the design of more specific clinical trials for testing interventions specifically tailored to patients with similar risk profiles. If researchers find that an infectious agent is an environmental trigger of the disease, efforts could be directed toward the development of a preventive vaccine. Alternatively, if a dietary component is found to be causative or protective, individuals at risk could take steps to either eliminate or add it to their diets. These are just a few examples of the enormously important and practical strides forward that can be envisioned and possibly attained once the underlying causes of type 1 diabetes are fully delineated.

Diabetes is an extremely costly disease to treat in both human and financial terms. It places an enormous burden on families and on the U.S. health care system. By pinpointing the constellation of type 1 diabetes disease genes, their environmental triggers, and their cascading effects on the immune system, researchers may be able to entirely prevent or reverse disease onset. Combating the disease at the front end is especially beneficial, because early steps could preclude or arrest the development of disease complications—including kidney failure, blindness, lower limb amputations, heart attacks, and strokes. Research on the underpinnings of the disease thus offers the real hope of preventing type 1 diabetes from ever ravaging the body. For individuals at risk, it would clearly be far better to completely prevent the disease than to undergo a difficult and suboptimal treatment regimen of daily insulin administration after the disease has begun wreaking havoc within the body. Likewise, the Nation as a whole would benefit from building a sound knowledge base for developing prevention-oriented strategies.



Katie and Ellie Clark:

Mother and Daughter Living with Type 1 Diabetes

Katie Clark spent weeks denying her 5-year-old daughter's symptoms of type 1 diabetes. Up to that point, Katie thought that the fact that everyone wanted to touch Ellie's beautiful curly blond hair would be her daughter's burden to bear. She was wrong.

When sugar was found in Ellie's urine on what was supposed to be her first day at a new preschool, Katie learned that Ellie had type 1 diabetes. Katie was devastated. She spent her 30th birthday at the hospital, and was deeply depressed for most of the next 2 weeks. She was also so very angry. "Anger isn't the most common emotion at the beginning," Katie observes. "However, we're not new to the disease. I've had type 1 diabetes for 28 years."

> ***"This is not the life I dreamt of for my precious daughter."***

At the time this profile was written, 10 months after being diagnosed, Ellie had already suffered many unwanted side effects from disease treatment. She had calluses on her fingers. Her bottom had scar tissue from her insulin pump sites. She had undergone 1,494 finger pricks and 98 pump site changes. Ellie's insulin pump site must be changed every three days. Ellie will ask, out of the blue, "Is it day three?" Katie laments, "I cannot tell you how heartbreaking it is for me to see my daughter worrying about an impending pump site change. There is relief on her face on those days when we can say, 'No honey, not today.' The devastation in her eyes is almost more than I can stand when we have to say, 'Yes, today is day three, sweetheart.'" Katie is concerned that "Ellie is spending her time worrying about diabetes when she should be playing with her baby dolls and learning to read."

One of the greatest difficulties Katie finds in dealing with Ellie's disease is knowing firsthand the challenges that Ellie will face as she grows up. Katie knows just how type 1 diabetes will affect every detail of Ellie's life. Katie states, "There is no escape...there are no vacations from type 1 diabetes." Ellie will have to endure constant finger sticks and worry about when her next meal will be. Like Katie, Ellie is at risk of developing devastating disease complications, such as blindness, kidney disease, and heart disease, which could ultimately reduce her life span by approximately 15 years. Katie recalls, "I can very vividly remember reading a magazine article about the complications of diabetes when I was 8 years old. I was horrified. I can see Ellie will be going through these same thoughts and dealing with these same issues, and it's horrible. This is not the life I dreamt of for my precious daughter."

Other less common but very memorable events will leave their imprint as well, as they have during some of the happiest moments of Katie's life. Recalling the insulin reaction she had on her wedding day, Katie laments, "My newly styled hair got messed up, and orange juice I needed to take immediately to adjust my blood sugar level was spilled on my veil." For each of her pregnancies, Katie saw her high-risk pregnancy obstetrician once a week, and in the months leading up to the births, she saw her doctors twice a week. While in labor, Katie was forced to check her blood sugar every hour. After

the births, the nurses whisked the babies away to check their blood sugar levels, because newborns of mothers with diabetes often have low blood sugar (hypoglycemia). The nurses had to put a tube down their throats to pump sugar into their stomachs to normalize their blood sugar levels.

Ellie's diabetes hits Katie and her husband particularly hard when they're tucking Ellie into bed at night. That's when she asks questions such as; "Mommy, why do some people get diabetes and some people don't?" Or she says, "Daddy, I don't want diabetes anymore." Katie and her husband face a new challenge, now that Ellie has begun school. "We have to teach Ellie's teachers how to take care of her," Katie observes.

> ***"I'd give everything I have—even my own life—for Ellie not to have to endure another day of this dreadful disease," Katie stresses.***

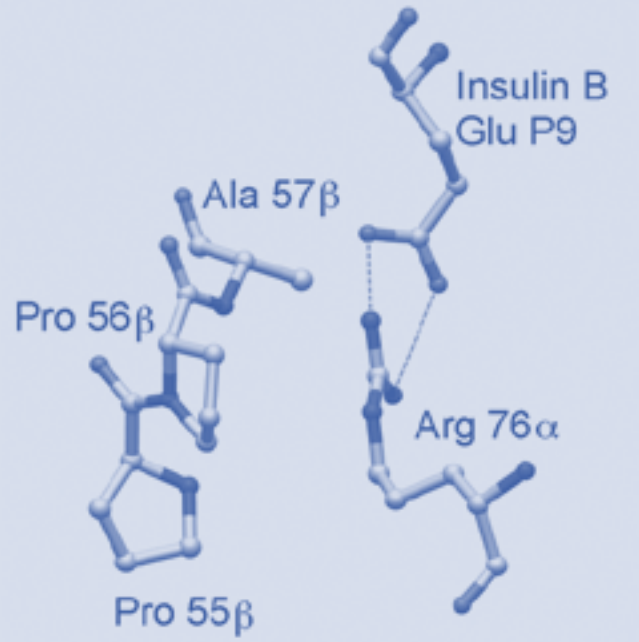
The Clarks dream of giving Ellie back the life she was living before her diagnosis and having a future brighter than one clouded by diabetes. "I'd give everything I have—even my own life—for Ellie not to have to endure another day of this dreadful disease," Katie stresses. "We must do everything we can to find a cure. Our sweet little girl with the curls deserves it."

Hope Through Research

In type 1 diabetes, a genetic predisposition for the disease is believed to be triggered by environmental factors. Researchers have already identified genetic regions that play a key role in disease development. However, there are other important genes that have not yet been identified, and it is still unclear how gene-environment interactions may promote the disease. Therefore, the NIH is supporting multifaceted research efforts to uncover important genes and environmental factors that promote the onset of, or confer resistance to, type 1 diabetes. For example, the T1DGC is a monumental effort to analyze the genetic makeup of families in which two or more siblings have type 1 diabetes to determine which genes confer disease susceptibility. Because not just a single gene "causes" type 1 diabetes, this type of large-scale effort is crucial to understanding the complex genetic underpinnings of the disease. Another example is a multicenter, multinational, NIH-funded epidemiological study called TEDDY. In this study, researchers are following newborns who are known to be genetically at risk for developing type 1 diabetes until they are 15 years old, to see who develops the disease. Researchers will use the population to pinpoint the environmental factors that either triggered the disease or provided protection from it. An NIDDK website describes opportunities for patients and family members to enroll in these and other type 1 diabetes clinical research studies: www.T1Diabetes.nih.gov/patient.

How will new knowledge about genes and environmental triggers help patients with type 1 diabetes, like Katie and Ellie Clark? The potential for this research to positively affect the lives of patients with type 1 diabetes is far-reaching. Genetic and environmental factors identified through these research efforts could be used as targets for researchers to develop novel disease prevention strategies. If a certain virus were found to contribute to disease onset, researchers could pursue the development of a vaccine against the virus. In addition, knowledge about which genes are passed down from one generation to the next will allow researchers to more easily identify who is at high risk for developing the disease, and therefore, intervene earlier in the disease process, before the destruction of insulin-producing beta cells even starts. Preventing disease onset means that children like Ellie would never have to endure the thousands of finger sticks or pump changes/insulin injections that are now part of their everyday lives. Disease prevention also prevents the development of life-threatening complications. Therefore, pursuing research on the genetic underpinnings and environmental triggers of type 1 diabetes has great potential for allowing children, like Ellie, to live the life that their parents dreamt for them.

Figure Legend: Three-dimensional representation of key amino acid interactions between insulin and a major histocompatibility complex (MHC) Class II molecule, DQ8, associated with a predisposition for type 1 diabetes. *(Image courtesy of Dr. Kai Wucherpfennig, Dana-Farber Cancer Institute and Harvard Medical School.)*



GOAL II:

PREVENT OR REVERSE TYPE 1 DIABETES

Why It Is Important To Prevent or Reverse Type 1 Diabetes

- Understanding Regulation of the Immune System
- Improving Screening for Type 1 Diabetes Risk
- Slowing the Immune Attack and Prolonging Pancreatic Function
- Reversing Type 1 Diabetes
- Enhancing Animal Models
- Developing a Safe and Universal Means for Primary Prevention

Patient Profile

- Jodie and Dillon Distel: Participating in Clinical Research To Fight Against Type 1 Diabetes

WHY IT IS IMPORTANT TO PREVENT OR REVERSE TYPE 1 DIABETES

Parents of children at risk for developing type 1 diabetes often ask: "Can research help my child lead a life free of this disease?" Those who are newly diagnosed ask: "If my body is still making some insulin, what can I do to prolong this or fully restore the ability to make it?"

Insulin treatment is essential for the survival of patients with type 1 diabetes, but it is not a cure. For the rest of their lives, patients must carefully watch their food intake, monitor their blood glucose levels, and try to control their levels with externally administered insulin. More serious than the inconvenience and discomfort of this treatment regimen is the danger of acute, life-threatening episodes of low blood glucose and the very high probability of chronic, disabling complications. To end these problems, researchers seek to short-circuit the underlying autoimmune disease process—that is, to thwart the immune system's misguided destruction of insulin-producing pancreatic cells.

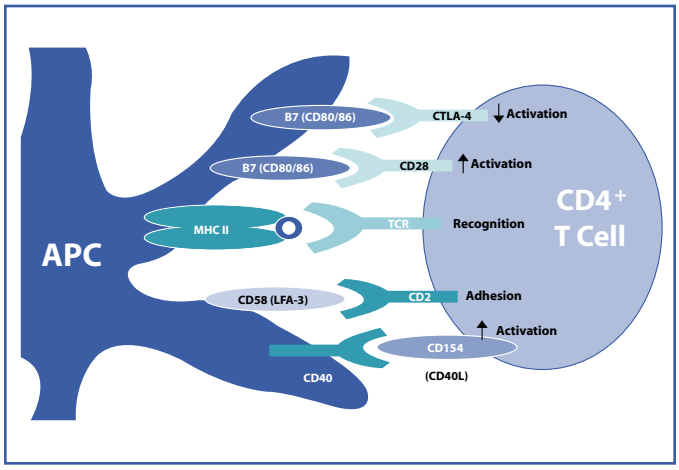
Because the genetic and environmental causes of type 1 diabetes are not well understood, strategies to prevent or reverse the disease are currently focused on intervening in the immune system's assault. These strategies must be two-pronged: they must squelch autoimmunity in people who are at risk for or already have the disease, while maintaining or restoring the patient's own insulin-producing capacity. (Goal III addresses another approach for reversing the disease by transplanting insulin-producing cells obtained from donor pancreatic tissue or regeneration of beta cells.)

Of course, the immune system provides critical protection against infection, so it is vital for any approach that modifies its activities to be as selective as possible in damping down just those processes that lead to autoimmunity. This delicate balancing act will be achieved by leveraging knowledge about the immune system in general, combined with insights into disease causation, in order to devise new diagnostic, treatment, and prevention strategies. Success will depend in large measure on building upon research advances and pursuing opportunities for uncovering the roots of this disease. Fortunately, research on type 1 diabetes has already advanced to the point that some new prevention and reversal strategies can be tested even in the absence of complete knowledge of disease causation.

Major progress has also been achieved through the identification of antibodies that are produced in type 1 diabetes when the immune system attacks the body's insulin-producing cells. These antibodies are, therefore, markers of type 1 diabetes. They have been shown to be detectable well before the loss of insulin production and the diagnosis of clinically overt disease. Tests of these antibodies in the siblings of patients with type 1 diabetes can predict with great accuracy whether they too will develop the disease in a few years. This predictive tool, coupled with other new technologies, has given researchers the remarkable ability to design and conduct primary prevention clinical trials in type 1 diabetes. A major research goal is to expand this type of predictive tool beyond its current, limited use in first-degree relatives of patients with type 1 diabetes.

Understanding Regulation of the Immune System

The immune system is made up of numerous different cell types that, when functioning properly, interact with one another to respond to various threats. Certain of these cells act to regulate the function of others. A central feature of that regulation is a process called "tolerance," recognition of self, which prevents the immune system from attacking the body's own cells. Tolerance is, therefore, a major focus of research on all autoimmune diseases, and scientists are making important strides in understanding how it works. Studies in special mouse and rat strains that have a genetic predisposition to type 1 diabetes have been insightful and will continue to contribute significantly to this research. While many forms of white blood cells play important roles in the autoimmunity of type 1 diabetes, researchers are homing in on the functions of one cell type, the T cell, which is thought to be instrumental in the autoimmune process, due to its destructive capacity combined with its potential to affect immune responses. For years, researchers have struggled to determine which beta cell proteins are key targets of autoimmune attack. Several published studies now support the notion that the insulin



T cells are thought to play a key role in the autoimmune processes that damage insulin producing beta cells. T cell activation requires two signals from an antigen presenting cell (APC): (1) the presentation of a peptide bound to class I or class II molecules of the major histocompatibility complex (MHC); and (2) binding of "costimulatory molecules" (such as B7) to receptors on the T cell. A possible therapeutic approach to preventing or reversing type 1 diabetes is to prevent T cell activation. One potential approach is to identify a way to block the second costimulatory signal.

(Image courtesy of Dr. George Eisenbarth and reprinted with the kind permission of Springer Science and Business Media. From Eisenbarth, S. "Primer: Immunology and Autoimmunity." Type 1 Diabetes: Molecular, Cellular, and Clinical Immunology. Ed. George S. Eisenbarth. Online Edition Version 2.5. Accessed at: www.uchsc.edu/misc/diabetes/oxch1.html. Copyright © 2004 Eurekah.com and Kluwer Academic/Plenum Publishers. All rights reserved.)

molecule itself is an important, potentially type 1 diabetes-initiating target of the immune system, although several other proteins may also play a role.

Improving Screening for Type 1 Diabetes Risk

Delaying or preventing type 1 diabetes can only be an effective strategy if health care providers are able to identify patients in the early stages of autoimmunity. Research has progressed to the point at which it is increasingly possible to identify people at risk for type 1 diabetes in the earliest stages of the disease, when a significant fraction of their insulin-producing cells is still alive and functioning. Current screening strategies look for proteins called autoantibodies, which characterize the autoimmune attack. Tests for genetic variants associated with type 1 diabetes are also incorporated into the screening process. With more precise genetic markers, screening methods that are currently applied only to relatives of patients with type 1 diabetes could conceivably be enhanced to predict and monitor disease risk in the entire pediatric population or the general population. Such genetic risk assessment would also shed light on other autoimmune diseases that often occur in patients with type 1 diabetes, including celiac disease, Addison's disease, and rheumatoid arthritis. As these screening tools are developed, the psychological impact of at-risk status and the most appropriate manner for communicating risk must be considered.

For those identified to be at risk based on antibodies and genetic susceptibility, monitoring the progression of disease and the effects of potential therapy is critically important. To this end, innovative clinical research studies will be made possible through a better understanding of facets of the immune response (e.g., regulatory T cells, innate immunity), which have recently been appreciated as key mediators of beta cell destruction. For example, it is important to understand cells that regulate the immune response, to develop better assays to measure the autoimmune response, and to find ways to measure the mass and function of insulin-producing cells. Tests of T cell function are under development as useful tools for monitoring autoimmunity. New imaging methods are also in development to detail the immune process in the pancreas. These methods may not only be excellent screening tools, but may also help scientists better understand the biology of autoimmunity.

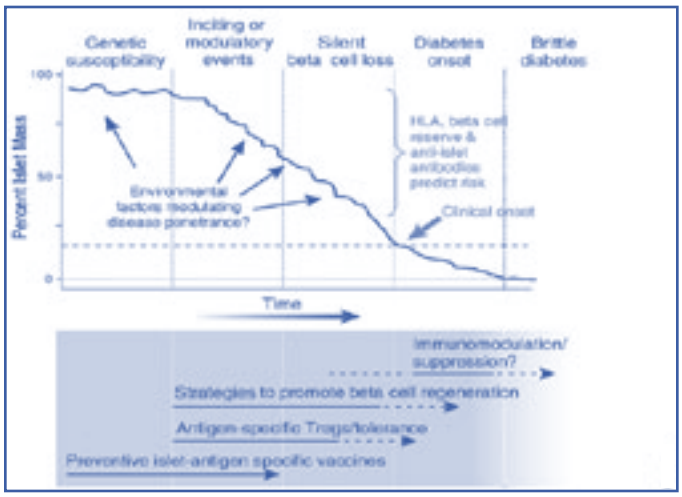
Slowing the Immune Attack and Prolonging Pancreatic Function

A more thorough understanding of genetic factors and environmental exposures underlying type 1 diabetes could lead to novel preventive approaches. At present, however, knowledge of causative factors is incomplete, and, therefore, strategies to prevent or reverse the disease are directed largely toward modulating the autoimmune process. A treatment that slows the immune attack and prolongs pancreatic functioning would be a great boon to patients because it could delay progression to diabetes and help those with the disease achieve better blood glucose control with less risk of hypoglycemia. Researchers are now testing several promising treatment regimens based on this approach. Particularly exciting research involves an agent known as anti-CD3, which has been shown to preserve metabolic function when administered to people with recent onset type 1 diabetes. With time, it is hoped that this, or other agents, will become proven components of a cure for type 1 diabetes by promoting disease reversal.

Reversing Type 1 Diabetes

For patients who have already developed type 1 diabetes, reversing or slowing beta cell loss is a key goal because prevention is no longer possible. Suppressing autoimmunity must

be a crucial component of any treatment designed to reverse type 1 diabetes in affected individuals. Once this suppression is accomplished, it may in principle be possible for patients to regrow pancreatic tissue. Indeed, data from the landmark Diabetes Control and Complications Trial suggest that some patients with type 1 diabetes maintain a limited capacity to produce their own insulin long after onset of disease. Additional recent research suggests that most people with type 1 diabetes, regardless of the length of their disease, may still have beta cells. These findings could mean that some beta cells are escaping the immune attack, and that their activity could possibly be bolstered. Alternatively, and perhaps more likely, the pancreas may be able to sometimes counter autoimmunity through a limited capacity for regeneration, although not nearly to a sufficient degree to actually offset beta cell losses. Unfortunately, many drugs that are known to be effective in suppressing the immune system (most commonly used in transplant patients) are actually harmful to beta cells, and may prevent regeneration. Therefore, researchers are attempting to develop new medications that are gentler and better targeted to the immune cells most directly responsible for beta cell autoimmunity. Medical approaches to stimulating beta cell development and function are addressed in Goal III.



Type 1 diabetes is a progressive autoimmune disease in which beta cells of the pancreatic islets are depleted by the immune system before the onset of clinical symptoms. Researchers suggest that a single intervention may not be completely effective; combinatorial therapies may be required. The proposed type of combinatorial therapies differs depending on the stage of the disease.

(Image courtesy of Dr. David Harlan and adapted with permission from Harlan DM and von Herrath M. Nature Medicine, 11: 716-718, 2005.)

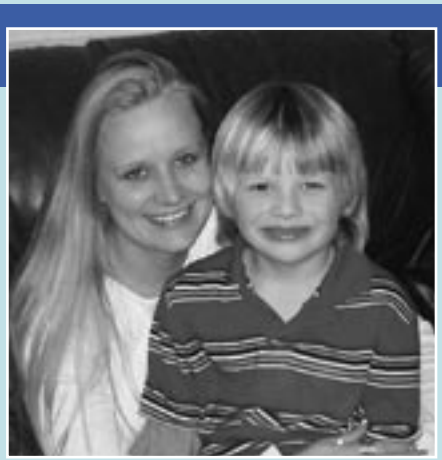
Progress would be furthered by the conduct of multiple clinical trials, based on sound infrastructural support and incorporating standardized design and outcome measures. Trials would assess not only drug efficacy, but also safety considerations, particularly the safety of agents that modulate or suppress the immune system. Once individual drugs are shown to be useful, it would also be beneficial to determine whether combination therapies offer improved outcomes. Additional studies could evaluate whether the preservation of insulin production in recently diagnosed patients offers short- and long-term clinical benefit with respect to complications, particularly eye, kidney, and nerve disease.

Enhancing Animal Models

Additional animal models are needed to accelerate the study of relevant immune mechanisms and potential interventions. While spontaneous animal models of type 1 diabetes have been very useful in understanding the mechanisms underlying development of the disease, some strategies that prevent it in animals have not proven successful in humans. Thus, mouse models that mirror the disease in humans with greater fidelity than do current models could be derived and tested for their utility to serve as surrogates for investigating new therapies aimed at combating autoimmunity. Such work would enhance the development of safe compounds for later testing in patients with type 1 diabetes.

Developing a Safe and Universal Means for Primary Prevention

Vaccination programs have dramatically cut rates of infectious diseases, such as measles, rubella, diphtheria, tetanus, mumps, and polio. These examples clearly show how prevention is more efficient and effective than treatment. With improved identification of environmental factors that modulate autoimmunity, potential targets for vaccination could be revealed for prevention of type 1 diabetes in humans.



Jodie and Dillon Distel:

Participating in Clinical Research To Fight Against Type 1 Diabetes

Jodie Distel had just given birth to her son, Dillon, at St. Joseph's Hospital in Denver, Colorado, when she was asked if she would like to participate in something called the Diabetes Autoimmunity Study in the Young, or DAISY. The study, she was told, would initially involve a fairly simple test: Blood from her newborn son's umbilical cord would be screened for genes that could indicate whether he was at high risk for developing type 1 diabetes.

"I didn't know very much about the disease," says Jodie, "but I figured that if taking part in the study might benefit someone else's child or my own son, that it was okay with me." She signed up for the study on the spot.

Within a week after Dillon's birth, Jodie was taken totally by surprise to learn that test results indicated that Dillon was at high risk for developing type 1 diabetes. Later, Jodie recalls, study staff alerted her that it was extremely likely that Dillon would have the disease by the time he was 8 years of age. In fact, exactly 3 days after his seventh birthday, Dillon was formally diagnosed as having the disease.

"I had no idea before taking part in the study that diabetes would be a factor in our lives," says Jodie. Now, looking back, she adds that, "Participating in DAISY is probably the best thing I've ever done for Dillon and his future!"

What Is DAISY?

DAISY is one in a group of epidemiological studies that researchers are pursuing to better understand the underlying causes of type 1 diabetes. The study is based at the University of Colorado Health Sciences Center in Denver. Marian Rewers, MD, the lead investigator for the study, says, "With DAISY, we have two primary objectives. One is to find out what causes [type 1] diabetes; the other is to find ways to prevent it."

To those ends, DAISY researchers are following two groups of children at risk for type 1 diabetes. One group was identified through screening a general population of newborns—which is how Jodie and Dillon got involved in the study. The other group consists of children who have a parent or sibling with type 1 diabetes.

"I had no idea before taking part in the study that diabetes would be a factor in our lives," says Jodie. Now, looking back, she adds that, "Participating in DAISY is probably the best thing I've ever done for Dillon and his future!"

Children who participate in DAISY are followed until they receive a clinical diagnosis of type 1 diabetes or until age 15, whichever comes first. Follow-up includes interviews with the parents to determine a child's diet and exposure to certain viruses, as well as periodic blood tests for three different antibodies against insulin-producing pancreatic islet cells, starting at 9 months of age. Like the initial genetic screening, the antibody tests are used to predict risk of developing type 1 diabetes. The presence of antibodies indicates that the autoimmune process has

begun. Dillon's blood tests were negative for antibodies against the insulin-producing islet cells until he reached the age of 2, at which time he began showing an elevated level of one antibody. Subsequently, his blood was tested more frequently, every 3 to 6 months. At three-and-a-half years of age, he began showing an elevated level of two antibodies. Other markers for diabetes began to change as well. Over time, Dillon's levels of a marker called hemoglobin A1c (HbA1c) began to show an upward trend. Finally, his blood sugar levels became elevated. On December 13, 2004, Dillon was diagnosed with type 1 diabetes. He started on a low dose of insulin, and is currently doing very well. As of January 2006, he has never been hospitalized for diabetes-related conditions. With only about one-quarter of the insulin dose it usually takes at his age, physicians are currently able to keep Dillon's levels of the HbA1c marker at a level consistent with improved long-term health outcomes in people with type 1 diabetes.

By participating in research studies that follow children from birth who are at high risk for type 1 diabetes, both the parents and children are better prepared if and when a child experiences onset of the disease.

Dillon's case appears to support previous observations that early diagnosis helps, to some degree, to preserve the body's insulin production. This may be in part due to avoiding a condition called diabetic ketoacidosis (DKA), a dangerous metabolic condition caused by profound insulin deficiency. Prior to diagnosis, many patients with undetected type 1 diabetes will develop DKA, which, if untreated, places them at risk of diabetic coma and death. However, the severe metabolic disturbance of DKA is not only life-threatening, but it also further damages any residual insulin-producing cells. Thus, early detection helped Dillon to avert both DKA and DKA's negative impact on his already compromised ability to produce insulin—and, by doing so, likely contributed to his need for less aggressive insulin therapy at diagnosis.

The benefits of early detection and preservation of the body's capacity to produce insulin can last many years. In the landmark Diabetes Control and Complications Trial, for example, participants who had preserved insulin secretion not only had better blood sugar control and lower insulin requirements, but also had a 50 percent lower risk of eye complications and a 65 percent lower risk of severe hypoglycemia, or low blood sugar (a risk patients face as a result of insulin treatment).

Thus, early detection of type 1 diabetes can provide both immediate and longer-term health benefits. "Dillon is in a much better situation than if we had not participated in the study," says Jodie. In addition to testing a child's blood for antibodies and elevated sugar levels, the families of the children who participate in DAISY are educated about what to expect in the way of symptoms, how to do blood sugar tests at home, and more.

As part of the DAISY research efforts, "one of the best things we do is to educate families, from the time their child's screening indicates high risk, straight through to diagnosis, if that should end up being the case," says Michelle Hoffman, RN, the clinical coordinator for DAISY.

Benefits of the DAISY Study

Since December 1993, the DAISY study has screened more than 33,000 newborns in the Denver, Colorado, area for genetic markers that would indicate high risk for type 1 diabetes. Of those, the study has followed more than 2,000 children whose genetic screenings indicated that they were at high risk for developing the disease. Of those, 143 children developed islet cell autoimmunity—a condition present in the majority of cases of type 1 diabetes, although people with islet cell autoimmunity do not always progress to onset of the disease. Of those 143, 48 have developed type 1 diabetes.[2]

"It should be noted," says Dr. Rewers, "that 90 percent of children in the United States diagnosed with type 1

[2] These numbers are current as of December 2005.

diabetes are hospitalized at the onset of the disease, and nearly one-third of those enter the hospital with DKA." According to Dr. Rewers, approximately 100 children die each year of DKA. However, of the 48 children in the DAISY study who went on to develop full-blown type 1 diabetes, only one—an 11-month-old infant—needed to be hospitalized at disease onset.

Therein lies one of the benefits for participants in the DAISY study: By participating in research studies that follow children from birth who are at high risk for type 1 diabetes, both the parents and children are better prepared if and when a child experiences onset of the disease.

Jodie lived for 7 years with the hope that Dillon would never be diagnosed with type 1 diabetes. However, when the diagnosis came, she was knowledgeable. "Because of the DAISY program, I think Dillon and I were prepared to handle Dillon's being diagnosed, and I think we had to go through far less than any other child and family who do not have the benefit of learning and recognizing early indications of this life-changing disease," she says. "From day one, I was told what symptoms to look for, and I mentally prepared myself for this day and how I would help Dillon from that day."

Because diabetes is an insidious disease, "most families are blindsided; they don't know what to look for to recognize onset of the disease," says Dr. Rewers. "When eventually diagnosed, the overwhelming majority of these children end up in the hospital, and many are fighting for their lives—at great emotional expense to themselves and their families, and financial expense to our society." He adds, however, that until researchers can discover and develop prevention strategies to arrest disease onset, they do not currently recommend extending screening programs outside of the research setting.

Research Findings

In addition to refining ways to recognize a genetic predisposition to diabetes and to pursue effective family follow-up, DAISY has been responsible for a number of significant findings. "For example," says Dr. Rewers, "by closely following these children, we've been able to rule out quite a few environmental factors once suspected as triggers for the onset of diabetes."

DAISY has also opened up new areas for investigation. For example, researchers are currently investigating whether the introduction of baby cereals may have something to do with the onset of inflammation in the pancreas that leads to diabetes. "We've discovered through DAISY that if babies at increased risk of type 1 diabetes first eat cereal regularly in their diets before 4 months of age, or after 6 months, their risk of islet autoimmunity is four to five times higher than if they begin eating cereal between 4 and 6 months of age," says Dr. Rewers. (The current American Academy of Pediatrics recommendation is to breast-feed babies and begin introducing iron-enriched solid foods, such as cereal, beginning at 6 months of age, if the child is ready [17].) For children who have a specific genetic marker that is known to strongly predispose individuals to type 1 diabetes, the risk appears to be even greater. According to Dr. Rewers, "These children have an overall increased risk of islet autoimmunity six times higher if fed cereal before age 4 months, and twelve times higher if cereal is delayed beyond 6 months, than if they are started on cereal at age 4 to 6 months." Research is ongoing to tease out the answers to this and other challenging issues regarding possible causes of type 1 diabetes and factors contributing to its onset.

> ***"The more brain power contributing to this effort, and the better we can coordinate our work and findings, the greater the chances of our discovering ways to more quickly develop prevention strategies for type 1 diabetes," says Dr. Rewers.***

TEDDY—A Collaborative Effort

In addition to DAISY, other studies have contributed

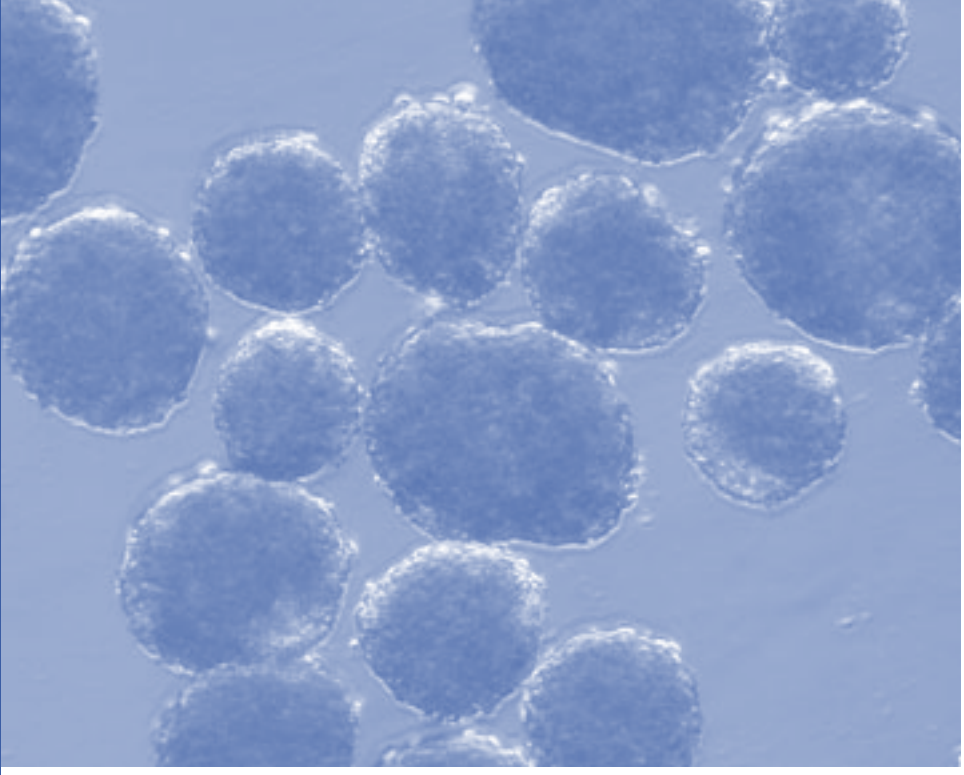
many important insights to advance research on environmental factors in type 1 diabetes. However, there are limitations to smaller studies, such as the number of patients that can be recruited in a given location. To overcome these limitations, the NIH spearheaded the launch of a long-term, international, collaborative effort to identify environmental triggers of type 1 diabetes. Begun in 2002, this effort is called "The Environmental Determinants of Diabetes in the Young," or TEDDY. Funded by the *Special Statutory Funding Program for Type 1 Diabetes Research* (see www.T1Diabetes.nih.gov), TEDDY consists of six centers in the United States, Finland, Sweden, and Germany. The creation of the TEDDY consortium allows for: a coordinated, multidisciplinary approach; collection of data and information in a standardized manner; greater statistical power than can be achieved in smaller studies; and the creation of a central repository that includes data and biological samples for use by the scientific community.

Researchers participating in TEDDY—including the Denver investigators who have conducted DAISY—are recruiting newborns who are genetically predisposed to developing type 1 diabetes. They are screening newborns from the general population, as well as newborns who have parents or siblings with the disease. The children will be followed until they are 15 years old or until they develop islet autoimmunity or type 1 diabetes. This long-term study will amass the largest data set and samples on newborns at risk for type 1 diabetes anywhere in the world.

"The more brain power contributing to this effort, and the better we can coordinate our work and findings, the greater the chances of our discovering ways to more quickly develop prevention strategies for type 1 diabetes," says Dr. Rewers.

TEDDY is currently enrolling patients. TEDDY enrollment sites in the United States are located in Georgia, Florida, Colorado, and Washington. For more information on enrolling in TEDDY, please see: www.niddk.nih.gov/fund/diabetesspecialfunds/t1d_ctcr/study.asp?StudyID=121

Figure Legend: Human islets. *(Image courtesy of Dr. Camillo Ricordi and Mr. Over Carera, University of Miami, Diabetes Research Institute.)*



GOAL III:

DEVELOP CELL REPLACEMENT THERAPY

Why It Is Important To Develop Cell Replacement Therapy

- Benefits of Cell Replacement Therapy
- Improving Islet Transplantation Techniques
- Fighting the Immune System's Destruction of Transplanted Islets
- Making New Beta Cells

Patient Profile

- Karla Edge: Islet Transplantation Brings New Hope to a Patient with Type 1 Diabetes

WHY IT IS IMPORTANT TO DEVELOP CELL REPLACEMENT THERAPY.

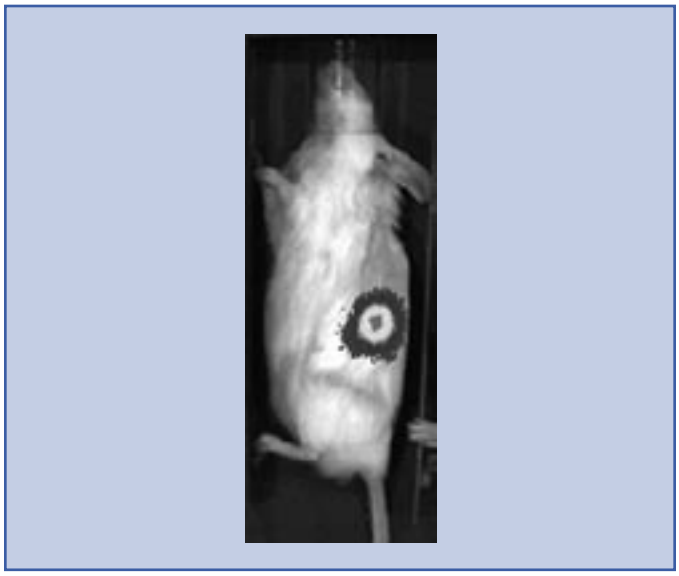
People who live with type 1 diabetes ask: "Will there be a cure for my disease? If cell therapy becomes available, will I be eligible? Are there side effects? How are scientists working to solve the problem of finding a source of insulin-producing beta cells so that all patients can someday receive an islet transplant?"

The prospects of a cure for type 1 diabetes have improved dramatically because of research advances in cell-based therapies. Using improved techniques, researchers are now capable of restoring substantial insulin production to patients with type 1 diabetes for a period of a few years by transplanting clusters of insulin-secreting beta cells. These cell clusters, called islets, are obtained from the pancreatic tissue of human organ donors. The transplanted cells are functional replacements for those destroyed by the disease through a misguided attack by the body's own immune defense system (autoimmunity). Unfortunately, this experimental procedure—called islet transplantation—is still limited for several reasons. First, there is not an adequate supply of donor tissue to treat all patients with type 1 diabetes who might benefit from this procedure if it were to become widely available in medical practice. Second, patients who receive islet transplants require lifelong medication to keep their immune systems from rejecting the new cells as "foreign." This regimen of immunosuppressive drugs has many unwanted side effects and is a major barrier that currently limits the study of islet transplantation to adults with brittle diabetes or those who already receive immunosuppressive drugs after kidney transplantation. If these and other barriers can be overcome, the standard of practice for treating type 1 diabetes could be revolutionized. Achieving the goal of developing safe cell-based therapy would dramatically improve the health and quality of life of type 1 diabetes patients. NIH-supported research is critically important for meeting these research challenges.

Benefits of Cell Replacement Therapy

Although research advances have improved the management of type 1 diabetes, patients often have difficulty controlling their disease. No matter how vigilant patients are, they cannot achieve the exquisite regulation of blood glucose levels that is provided by a healthy pancreas. When the body's blood glucose level is not properly balanced, health complications of diabetes arise sooner and have more devastating effects over time (if glucose is too high), or an individual can become shaky, sweaty, and confused; lose consciousness; and even die (if glucose is too low). Therefore, researchers are working on ways for patients to improve control and avoid these complications. Replacing the insulin-producing pancreatic beta cells that have been destroyed by the disease would enable the body to assume its normal role of precisely regulating blood glucose levels. Patients would no longer have to check their blood glucose levels with finger sticks, inject themselves with insulin, worry about when to eat their next meal, or be plagued by the fear of life-threatening bouts of dangerously low blood glucose (hypoglycemia). Furthermore, islet transplantation can achieve the tightly regulated blood glucose control that has been shown to slow or prevent the development of long-term disease complications. In short, realizing this goal would enable patients to live a life free of the everyday burden of this disease and to be spared from developing life-threatening disease complications.

Significant progress in islet transplantation has been achieved in recent years. Several research centers have shown, on a modest scale, that people with type 1 diabetes who receive transplanted islets can remain free of insulin injections for substantial periods of time. However, major challenges must be overcome before large-scale implementation of islet transplantation will be feasible. First, the methods of acquisition and delivery of islets must be optimized in order to provide replacement therapy for all people suffering from type 1 diabetes. This includes refining the islet transplantation procedure to avoid complications, such as bleeding. Second, clinical treatments must be developed that will better combat the body's tendency to destroy transplanted islets. Third, the mechanisms of pancreatic beta cell development must be elucidated to facilitate methods for producing cells in sufficient quantities to provide an adequate supply for transplantation. Finally, safer methods of preventing rejection and recurrent autoimmunity must be developed so that the benefits outweigh the risks for patients who do not have exceptionally brittle diabetes with recurrent hypoglycemia.



In vivo imaging of islets: A mouse was transplanted with 1,000 islet equivalents of human islets expressing a luminescent marker. Non-invasive, bioluminescence imaging was performed on the anesthetized mouse, and the transplanted islets could be easily visualized.

(Image courtesy of Dr. Alvin Powers, Vanderbilt University.)

Improving Islet Transplantation Techniques

In current methods of islet transplantation, insulin-producing cells are taken from a donor human pancreas and transferred (or grafted) into an adult patient, most commonly in the liver. Once implanted, these grafts begin to make and release insulin in response to the body's needs. The transplanted cells thus enable the patient's efficient use of glucose for energy and keep the level of glucose in the blood finely balanced. The goal is to transplant a sufficient quantity of insulin-producing cells to keep the blood glucose level as close to normal as possible—with little or no reliance on external insulin administration.

Researchers have confirmed that islet transplant recipients are able to maintain near normal blood glucose levels, which is the primary and most highly desired outcome. However, they also have observed that success of the transplantation process varies greatly and wanes over time, underscoring the need for further research on methods of obtaining islets for transplantation and maintaining functioning transplanted islets. Progress has also been made in developing laboratory tests to ensure that high-quality islet cells are used for transplantation and in refining the technique for implanting donor islets into patients—both of which are key to optimizing the success of the treatment.

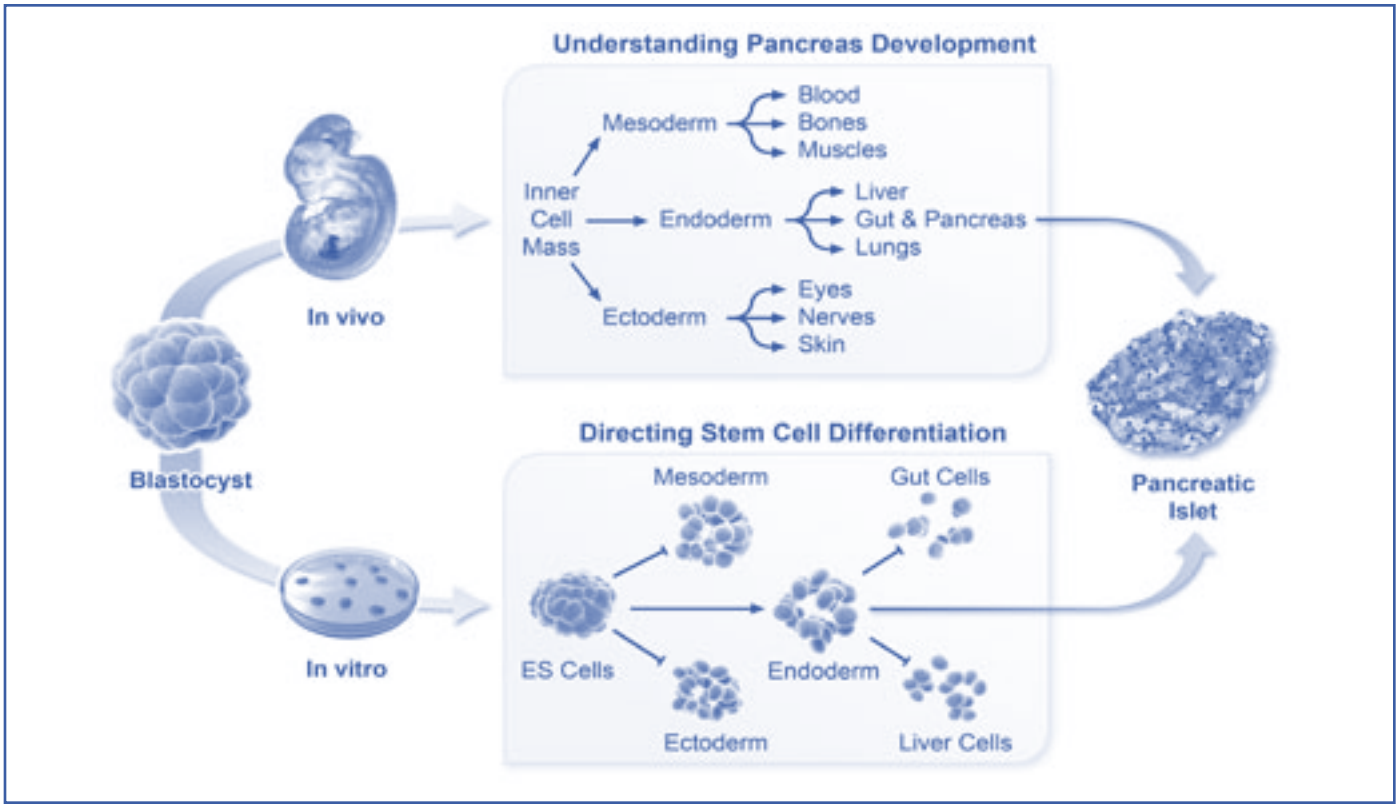
Limitations remain for the expansion of the islet transplant technique. For example, during the many steps that occur prior to the transplant surgery, the fragile islet cells must be collected and handled very carefully so as to preserve their health and function. Improper handling of cells renders them of little benefit to the patient. Likewise, these healthy donor cells must be implanted into the patient in an environment that continues to promote good health and function. Many of the complex details of what constitutes this type of environment are not yet completely defined. Scientists are investigating alternative surgical sites, as well as sophisticated biomaterials that may protect the islet graft from destruction by the immune system. Improving the collection and transplantation methods for islets is crucial for immediate expansion of the technology. If cell survival is enhanced, a lower number of cells is required, and thus a greater number of patients can undergo this life-altering treatment. To reach the goal of improving islet transplantation, future research will need to focus on improving the processing and handling of islets, developing techniques to measure viability and predict success of the islets prior to transplant, and developing and refining islet transplant techniques.

Fighting the Immune System's Destruction of Transplanted Islets

Patients who undergo islet transplantation are required to take lifelong medications to prevent the immune system from attacking and destroying the transplanted cells. However, these drugs can cause serious and adverse side effects, can reduce the body's ability to fight infections, and also may weaken or kill the grafted cells. Researchers are gaining a deeper understanding of the concept of graft rejection and how to identify early signs of rejection, at a point when intervention is possible. It is not only important to prevent rejection, but recurrent autoimmunity must also be overcome. Researchers have developed less toxic agents to block the immune attack on the transplanted islets. These agents will soon be tested in a limited number of islet transplant recipients. In these pilot clinical trials, researchers will study new approaches to help ensure that all patients who undergo treatment have the greatest opportunity to achieve successful results. To reach the goal of reducing immune rejection and recurrent autoimmunity, future research could focus on developing novel immunomodulation strategies and technologies, as well as on creating techniques capable of monitoring and preventing autoimmunity and rejection.

Making New Beta Cells

A major restriction of islet transplantation is tissue supply, which is currently limited to donor pancreatic tissue.



Embryonic stem (ES) cells hold significant potential for deriving differentiated cell types, including insulin-producing beta cells. Knowledge of genes and signals controlling pancreatic development in the whole animal can enable test tube recapitulation of specific embryonic programs in stem or progenitor cells to produce functioning insulin-producing cells for replacement therapy in type 1 diabetes.

(Figure courtesy of J.P. Cartailler, Beta Cell Biology Consortium.)

However, research is under way to develop methods to regenerate beta cells within the pancreas or to generate beta cells from stem/progenitor cells. If successful, these methods could lessen or obviate the reliance on donor pancreatic tissue as a source of transplantable cells.

Researchers have accumulated considerable knowledge about the basic biology of pancreatic beta cells, in terms of how these cells function and how they are affected in type 1 diabetes. Methods have been developed to study the genes that are uniquely active in beta cells and the proteins those genes produce. Knowledge is expanding about stem/progenitor cells that differentiate into insulin-producing beta cells. Studies have suggested that it may be possible to coax the small number of insulin-producing cells that might remain in individuals with type 1 diabetes to multiply and once again produce insulin. Of course, overcoming ongoing islet cell damage in diabetes would also be required to explore possibilities for regenerating beta cells or for boosting residual beta cell function.

Much remains to be discovered about the body's insulin-producing beta cells, as well as the stem cells from which they are derived. Specifically, the genes, proteins, and other biological compounds associated with beta cell development and the signals required for their maintenance and expansion must be elucidated. These studies could permit scientists to grow islet cells for use in future research efforts and help them recreate an environment in the transplant patient that would optimize the success of the grafted islets. This knowledge is also key to efforts to regenerate beta cells in the pancreata of patients with type 1 diabetes.

Islet transplantation is a promising therapy that can yield long-lasting and beneficial results for people with type 1 diabetes. Significant progress has been made in expanding the knowledge of islet cell biology and the processes associated with transplantation and immune rejection. However, the clinical strategy remains limited due largely to constraints in islet supply and the side effects of the drugs needed to prevent rejection and recurrent autoimmunity. Future research is needed to make islet transplantation a viable therapeutic strategy for more individuals suffering from type 1 diabetes. Addressing islet transplantation technologies, immune modulation, and beta cell development will permit researchers to move closer to a cure.

Karla Edge:

Islet Transplantation Brings New Hope to a Patient with Type 1 Diabetes

Karla Edge was diagnosed with type 1 diabetes in 1967, at age 6. As a child, her disease was relatively free of complications. However, at age 13, she started having life-threatening hypoglycemic episodes. By the time she reached middle age, the episodes had become much more frequent and severe, to the point that she was experiencing several episodes a week.

"My blood sugar was so out of control that I couldn't go anywhere by myself," says Karla. Her husband, Mike, as well as other family members and friends, felt the need to call her at all hours of the day to make sure she was okay. Her two young daughters, Talia and Tatum, worried constantly about their mother. "It was all so very scary. I felt like I was knocking on death's door," says Karla.

Living with Type 1 Diabetes

Type 1 diabetes results when the body's immune system destroys the pancreatic insulin-producing beta cells that control blood sugar levels. As a result, people with type 1 diabetes fight a constant battle to keep their levels from going too low or too high. Yet, even those who manage their diabetes well—by controlling their dietary intake and taking daily injections of insulin—are at high risk for a wide range of complications, including heart disease, stroke, blindness, kidney disease, and nerve damage.

Fortunately, 45-year-old Karla has no organ complications whatsoever as a result of her diabetes, and, "My eyesight is perfect," she says proudly. However, she developed high blood pressure during her first pregnancy, but manages to keep it under control with medication. What she wasn't able to keep under control, no matter how hard she tried, were her blood sugar levels.

A Roller Coaster Ride

When she was 18 years old, Karla went into convulsions as a result of her low blood sugar. She was taken to the hospital in an ambulance. By the time she arrived in the emergency room, her blood sugar count had dropped to 10 mg/dL. A normal blood glucose level is approximately 100 mg/dL. Karla was told that she was lucky. Just the week before, another young woman had come into the hospital with a blood sugar count of 16 mg/dL and had died.

"My blood sugar was so out of control that I couldn't go anywhere by myself," says Karla.

Since that time, Karla's life has been a roller coaster ride. She was fine as long as her blood sugar was in the normal range. But when it suddenly dropped, she would become disoriented, start slurring her words, and her eyes would dilate. "I looked crazed," she says. Karla often had to rely on close friends to give her glucose tablets to bring her blood sugar back up and to make sure she got home all right. The disease was taking an emotional toll on her family, as well. She recalls a time when she was standing in a department store checkout line with her then 6-year-old daughter. "My daughter looked up at me and knew I was in trouble. She urgently told the person standing next to us, 'Please, my mom is a diabetic and she needs help.'"

Her diabetes affected her working life, as well. Karla worked as a data entry operator and was often late for work as a result of her hypoglycemic episodes. Her boss didn't understand the severity of Karla's condition and wasn't sympathetic to her being late or staying home from work. Over the years, the disease's impact on Karla's body—plus the emotional stress at work—had become so intense that her primary care physician strongly recommended that Karla retire early from her job, which she did at age 42.

It was about that time that Karla's sister, Kathy, read a newspaper article about an experimental treatment for type 1 diabetes, called islet transplantation, offered by the Diabetes Research Institute (DRI) in Miami, Florida. Karla immediately contacted the DRI, filled out an application, and was told she was a perfect candidate for the procedure. Although she had to wait nearly 3 years before undergoing her islet transplant, she says that it was well worth the wait.

Because islet transplants are experimental, they are available only to people who meet specifically defined criteria stated in the study protocol. To date, only adults with severely unmanageable blood sugar levels or who have already undergone a kidney transplant have been eligible.

Undergoing a Life-Changing Islet Transplant

In September 2005, Karla underwent a revolutionary new procedure for islet transplantation, called the Edmonton Protocol. Originally developed by researchers at the University of Alberta in Edmonton, Canada, the protocol uses a novel, steroid-free combination of three drugs that appears to prevent rejection, as well as halt autoimmune destruction of transplanted islets. Islet transplantation replaces the islets that have been destroyed by type 1 diabetes with islets from a donor cadaveric pancreas. The donor islets are infused through a catheter (small tube) into the portal vein of the liver. In a successful transplant, the new islets start producing insulin—eliminating or reducing the need for patients to take insulin. In effect, islet transplantation could be considered a real "cure" for the disease.

"I remember days, before the procedure, when I felt like I was 120 years old. Now I feel like I'm back in my 20s again. It's wonderful. No, it's a miracle!"

Karla's transplant was performed on September 19, 2005. She went into the procedure at about 2:00 p.m. and was given a local anesthetic, which meant she was awake throughout the entire procedure. She reports having felt very little pain or discomfort from the procedure itself and was back in her hospital room by 4:30 p.m. and released from the hospital the next day. Because the transplanted islets started working immediately, her physician reduced her insulin dosage that first day. Within 2 weeks, Karla was totally insulin-free. "It was the first time since I was 6 years old that my body produced enough insulin naturally to keep me alive," she says. "I'm very grateful to Dr. Rodolfo Alejandro, Director of Clinical Islet Transplantation at the DRI, as well as Drs. Tatiana Froud and David Baidal for their kindness and expertise," says Karla.

A New Beginning

After undergoing the islet transplant, Karla felt that her future had arrived. At the time this profile was written, she was insulin-free and says that the transplant has been a life-changing event for her for the better. "I never knew I could feel so good," says Karla. "It's amazing!"

Karla still needs to check her blood sugar before meals and two hours afterwards, as well as at bedtime. "It's always normal," she says with great relief. "It's nothing like it was before, when I had to check it every time I left the house or got in the car to drive somewhere." She

also no longer needs to eat on a regimented schedule. Moreover, she can now do volunteer work at her daughters' school without concerns about episodes of severe low blood sugar.

It has been an enormous relief for her family, as well. "Before the procedure, my husband would wake me up in the middle of those nights when I would go into a hypoglycemic convulsion, and he would have to give me an emergency injection of glucagon to prevent me from going into a diabetic coma and perhaps dying. This would happen at least once a month. He says that now he can sleep well at night, without having to worry about me."

As with any transplant, rejection is a major concern. The immune system is programmed to destroy bacteria, viruses, and tissue it recognizes as "foreign," including transplanted islets. Immunosuppressive drugs are needed to keep the transplanted islets functioning. These drugs, however, come with potentially serious side effects. Fortunately for Karla, her body has handled them well. "Aside from experiencing some nausea when I was in the hospital, I don't remember the last time I felt sick from the drugs." Nor, she adds, has she experienced any other side effects.

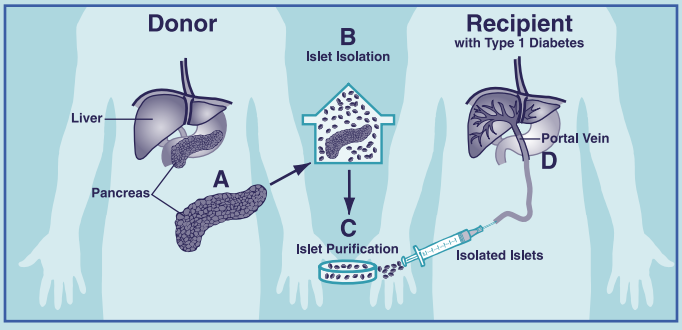
While the experiences of islet transplant recipients can vary, Karla's reactions have been very positive. Karla adds: "I remember days, before the procedure, when I felt like I was 120 years old. Now I feel like I'm back in my 20s again. It's wonderful," she says joyfully, and then pauses. "No, it's a miracle!"

Future Research: The Quest To Make Islet Transplantation a Viable Treatment Strategy for Patients with Type 1 Diabetes

The demonstrated success of the Edmonton Protocol has engendered new hope for people with type 1 diabetes. It has also benefited patients, such as Karla. However, islet transplantation using the new protocol is still very much in its infancy. For example, people who undergo a transplant may not be able to tolerate the immediate side effects of the immunosuppressive drugs, and the potential long-term side effects are not fully known.

The Collaborative Islet Transplant Registry analyzed outcomes in 138 patients at 19 medical centers in the United States and Canada. Data analysis showed that 58 percent of recipients no longer had to inject insulin 1 year after their last islet infusion; in 19 recipients, the donor islets failed to function. These data show that not every recipient becomes insulin-independent after undergoing this procedure. In addition, because islet transplants are experimental, they are available only to people who meet specifically defined criteria stated in the study protocol. To date, only adults with severely unmanageable blood sugar levels or who have already undergone a kidney transplant have been eligible.

Further research is needed to overcome the current barriers in the field of islet transplantation. To propel research progress, the NIH is supporting multifaceted research efforts, primarily with support from the *Special Statutory Funding Program for Type 1 Diabetes Research*. Major goals are to increase the number of islets available for transplantation and to reduce or eliminate the need for immunosuppressive drugs after transplant. For example, the NIH launched a major new Clinical Islet Transplantation Consortium, which is conducting multiple islet transplantation trials to improve methods of



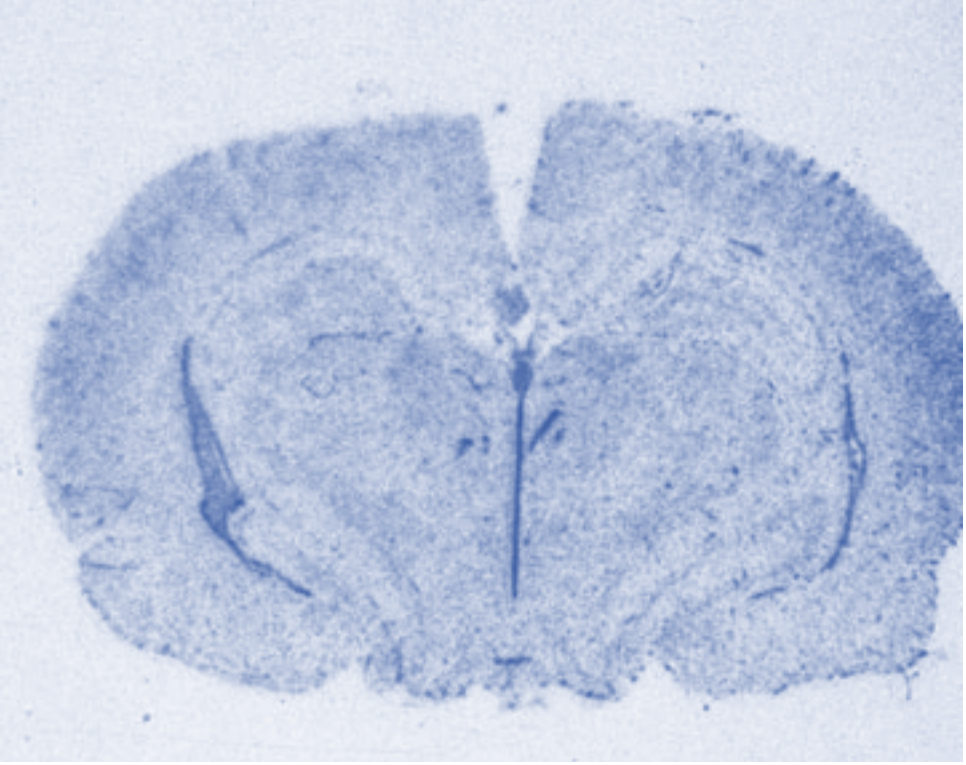
Islet transplantation is an experimental procedure in which islets are isolated (B) and purified (C) from a donor pancreas (A) before infusion into the portal vein of the recipient's liver (D). If the transplant is successful, the new islets begin producing insulin in a regulated manner, thereby eliminating or reducing the patient's need for insulin administration.

isolating islets, improving techniques for administering the transplanted islets, and developing approaches to minimize the toxic effects of immunosuppressive drugs. The Islet Cell Resource Centers are a key resource for providing islets to the broad scientific community for use in both clinical islet transplantation and basic research studies. The Non-human Primate Transplantation Tolerance Cooperative Study Group is evaluating novel methods to induce immune tolerance to transplanted islets in non-human primates to achieve long-term graft survival. This tolerance induction approach would avoid the need for lifelong immunosuppressive therapies. To tackle the shortage of islets, researchers in the Beta Cell Biology Consortium (BCBC) are collaboratively working to understand beta cell development and function, in order to identify ways to grow unlimited numbers of beta cells in the laboratory that can be used to treat patients. Research is also under way in xenotransplantation, which studies the possible use of non-human organs (such as from pigs) for transplantation into humans.

In addition to research on islet transplantation, the NIH also supports research on other methods to replace the insulin-producing beta cells that are destroyed in type 1 diabetes. Recent studies have shown that people with long-standing type 1 diabetes have some remaining functional beta cells. Therefore, research on the mechanisms controlling beta cell growth and regeneration, such as those being pursued through the BCBC, could lead to novel therapies designed to stimulate beta cell growth in the body.

Through islet transplantation, Karla Edge has re-experienced life without the need for daily insulin administration. It is only through additional research efforts that Karla's life-changing, positive experience may become a reality for many more patients with type 1 diabetes who could potentially benefit from islet transplantation.

Figure Legend: Glucose must cross the blood-brain barrier to be used by the brain as fuel. Transport of glucose across the barrier is mediated by a protein called GLUT1. Analyses of GLUT1 gene expression in brain sections from rats have shown that GLUT1 is expressed at higher levels in the brains of hypoglycemic animals. *(Image courtesy of Dr. Ian Simpson and reprinted with permission from Simpson IA, et al. J Neurochem. 72: 238-247, 1999. All rights reserved.)*



GOAL IV:

PREVENT OR REDUCE HYPOGLYCEMIA IN TYPE 1 DIABETES

Why It Is Important To Prevent or Reduce Hypoglycemia In Type 1 Diabetes

- Sensing Low Blood Glucose
- Preventing Hypoglycemia-Associated Autonomic Failure (HAAF)
- Protecting the Brain
- Building an Artificial Pancreas

Patient Profile

- The Beauregard Family: What It Is Like To Care for a Young Child with Type 1 Diabetes

WHY IT IS IMPORTANT TO PREVENT OR REDUCE HYPOGLYCEMIA IN TYPE 1 DIABETES

Patients with type 1 diabetes walk a tightrope. Every time they check their blood glucose and adjust their insulin, they must balance the immediate danger of low blood glucose and the long-term risk of complications from high blood glucose. They worry, "What if insulin therapy makes my blood glucose level drop dangerously low and I'm not even aware of it? Will I go into a life-threatening coma as a result? Who will even know this is happening, and will they be able to help me?" Similar questions haunt the parents of young children with diabetes—many of whom cannot sleep at night because they are standing watch at their child's bedside. Facing an episode of dangerously low blood glucose—known as hypoglycemia—is one of the greatest fears of patients with type 1 diabetes and their families. Thus, an urgent research goal is to find ways to prevent or reduce this acute danger of insulin treatment.

Insulin therapy is a life-saving treatment for people with type 1 diabetes. However, it is sometimes difficult for patients to gauge the exact amount of insulin that they should administer to themselves at any given moment to meet their body's needs. Some patients use pumps that deliver insulin, but these devices have not yet been developed to the point where they can sense and respond to the body's need for insulin.

If there is too much insulin in the body, it increases the risk of hypoglycemia, or low blood glucose. When blood glucose levels fall below a minimal threshold, serious and life-threatening consequences can result. Moreover, after a few episodes of hypoglycemia, patients with type 1 diabetes can lose the ability to sense drops in blood glucose levels, a condition called hypoglycemia unawareness. Therefore, they are at increased risk of additional hypoglycemic episodes. This risk is even greater at night, especially for children, causing anxious parents to go without sleep themselves so they can monitor their children for signs of low blood glucose levels. Adults with type 1 diabetes also worry about hypoglycemia unawareness. Those who have ever experienced severe low blood glucose episodes are especially fearful. Unfortunately, these fears can lead them to abandon a regimen of intensive management, even though research has demonstrated its benefit in preventing or delaying the heart, eye, nerve, and kidney complications of diabetes. Clearly, research that leads to new or better ways to prevent or reduce low blood glucose could profoundly improve the health and well-being of people with type 1 diabetes and their families.

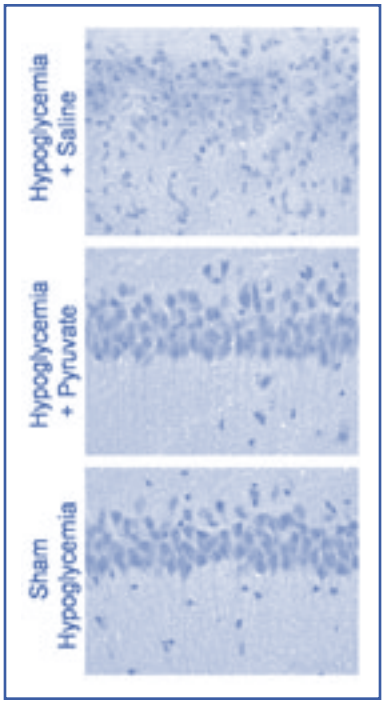
Researchers are attacking the problem of low blood glucose from several angles. They aim to understand how the body and brain normally communicate about blood glucose levels, as well as to identify what parts of this communication network are damaged or impaired in people with type 1 diabetes. An important tool for research in these critical areas will be animal models of disease. Through a multifaceted approach, researchers hope to more rapidly achieve the ultimate goal of preventing or reducing hypoglycemia in patients with type 1 diabetes. They are asking several questions: How do recurring hypoglycemic episodes impair a patient's awareness of impending low blood glucose levels and resulting hormonal responses over time—a vicious cycle called "hypoglycemia-associated autonomic failure," or HAAF? How can a patient's brain adapt to protect itself from low blood glucose damage? What new clinical approaches would minimize the risk of low blood glucose, such as technologies that could integrate glucose level sensing and insulin delivery? Can effective educational, behavioral, and clinical strategies be developed to prevent or reduce hypoglycemic episodes?

Sensing Low Blood Glucose

Understanding how the brain and body work together to determine and adjust blood glucose levels is a complex undertaking, but researchers have made significant progress in the past decade. Scientists now know that glucose-sensing cells are stationed within the brain and in key blood vessels outside of the brain that pick up signals and send them to the brain.

They also know more about how those cells are "wired" to the brain, so that it can receive continuous information about blood glucose levels. New insights are emerging about how the brain integrates this input with other metabolic signals it receives to develop the best response to keep blood glucose levels in a normal range.

Now that researchers have a big picture, they are seeking the details of the body's sensing apparatus and how it is affected by having type 1 diabetes. The underlying disease and insulin therapy may also alter the levels of other metabolic signals, thereby affecting how the brain responds to signals of low blood glucose levels. By identifying the mechanisms and other factors involved, researchers will be better positioned to develop effective clinical interventions to prevent precipitous drops in blood glucose in patients. Already, blood glucose awareness training for patients with type 1 diabetes has demonstrated dramatic benefits. Patients improved in their ability to detect high and low blood glucose levels and adjust their glucose accordingly. It is important to find ways to disseminate and implement these positive findings so that more patients can benefit.



Severe hypoglycemia can lead to death of neurons in the brain. In one study, hypoglycemia was induced in rats (top 2 panels) but not induced in the control rats (bottom panel). Hypoglycemia was terminated by treatment with glucose alone (top panel) or glucose plus pyruvate (middle panel). Analysis of hippocampal brain sections 7 weeks after the hypoglycemic injury showed that the rats treated with glucose plus pyruvate had less neuronal death than rats treated with glucose alone, suggesting that pyruvate may protect neurons from death due to severe hypoglycemia.

(Image courtesy of Dr. Raymond Swanson. Copyright © 2005 American Diabetes Association. From Diabetes, Vol. 54, 2005; 1452-1458. Reprinted with permission from The American Diabetes Association.)

Preventing Hypoglycemia-Associated Autonomic Failure (HAAF)

What contributes to the recurring nature of hypoglycemic episodes and increasing unawareness that an episode is about to strike? Normally, a drop in blood glucose triggers the body's warning system to release stress hormones, including adrenaline, and to stimulate a part of the nervous system that raises glucose and results in such symptoms as nervousness, shaking, and sweating. These warning symptoms help make people aware that they need to eat or take other steps to increase their blood glucose levels. The body also reacts with other "counter-regulation" defense measures, including the release of a hormone that elevates blood glucose (glucagon). However, in people with type 1 diabetes, these alert mechanisms and defense measures are significantly impaired and worsen with each episode of low blood glucose.

Being unaware of plummeting blood glucose levels is both dangerous and frightening. Moreover, patients are faced with the difficult fact that using insulin therapy to tightly control blood glucose levels and improve health in the long term increases their risk of severe and worsening low blood glucose episodes in the short term. Although the HAAF syndrome can be reversed by as little as several weeks of scrupulous avoidance of low blood glucose levels, it is difficult to accomplish this without losing good control of blood glucose levels and, thus, losing the benefits of this control, such as preventing long-term complications. Thus, it is critically important to identify the as-yet unknown mechanisms responsible for hypoglycemia unawareness so that new clinical strategies can be developed to combat HAAF, while simultaneously improving or maintaining good blood glucose control.

Future research will be focused on new strategies to prevent or reverse the HAAF syndrome. To do this, researchers will need to focus on three major objectives. First, they will need to identify how low blood glucose causes HAAF to develop, by studying this syndrome in animals. Animal models will also be important for research that can lead to preventive therapies. Second, researchers will need to use multiple tools to study what is happening in the brains and bodies of people affected by HAAF and how it affects their management of diabetes. For example, brain imaging studies combined with hormone measurements could help researchers understand why patients are so vulnerable to hypoglycemia while they sleep or when they need to perform complex tasks. Finally, studies should focus on ways to restore the body's innate ability to counter low blood glucose levels with defense mechanisms that elevate blood glucose.

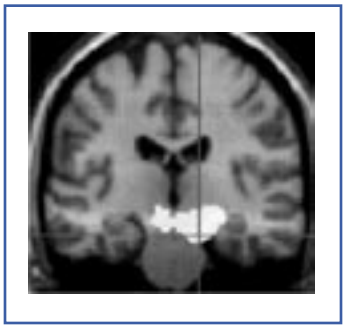
Protecting the Brain

The brain is almost entirely dependent upon blood glucose for the energy it needs to work. This dependency makes the brain quite vulnerable to episodes of low blood glucose. While it is crucial to discover ways to prevent these episodes in the

first place, it is equally important to pursue therapies that patients can use to protect the brain from injury due to low blood glucose.

Developing effective new therapies will require knowledge of how the brain acts to obtain a constant fuel supply, and what it does to protect itself when its major fuel, glucose, is in short supply. Studies are providing insights about the alternate fuels and fuel reserves that the brain uses when blood glucose is in short supply and are showing that patients with type 1 diabetes may use alternate fuels more efficiently. More is now known about how glucose and other fuels move from the blood into the brain. Now, emphasis needs to be placed on identifying the specific changes that occur in the brain in the face of low blood glucose and on determining which of these are the most important to exploit for therapeutic intervention—both to reverse brain injury and to promote protection from brain injury. For example, if use of alternate fuels is an effective way for the brain to protect itself from injury, then patients could take agents to increase those fuel supplies.

It appears that the brain's mechanisms for enhancing fuel efficiency and protecting itself from injury create a catch-22 situation—while protecting the brain from immediate injury, they seemingly "hide" low blood glucose levels from the patient, contributing to hypoglycemia unawareness. During a hypoglycemia episode, there is impairment in the patient's cognitive function—the higher-order brain processes, like thinking and memory. However, once the episode is over, it is not clear if there are long-term impairments. This picture is even more complex because insulin therapy itself may also directly affect cognitive function. Researchers are exploring these factors to better understand and prevent cognitive impairment in patients.



The image depicts a composite analysis of brain imaging studies of type 1 diabetes patients with or without hypoglycemia unawareness, at either normal or low glucose levels. The white portion represents an area of the brain known to contain glucose-sensing cells in which differences in the uptake of a labeled form of glucose is observed in the two patient populations. Patients with hypoglycemia unawareness had lower glucose uptake. These data suggest altered glucose uptake, metabolism, or both, in this brain region, which is associated with hypoglycemia unawareness.

(Image courtesy of Drs. Stephanie Amiel and Laurence John Reed. Copyright © 2001 American Diabetes Association. From Diabetes, Vol. 50, 2001; 2329-2336. Reprinted with permission from The American Diabetes Association.)

Building an Artificial Pancreas

Insulin therapy has improved tremendously over the past two decades, contributing to longer life and better quality of life for patients with type 1 diabetes. New forms of insulin, combined with new technologies for blood glucose measurement and portable "pumps" for insulin delivery, have enhanced the ability of patients to manage their blood glucose levels. Yet, current therapies to administer insulin are still inadequate substitutes for the body's own exquisite mechanisms for sensing and responding to insulin needs—mechanisms that are destroyed in type 1 diabetes. One major goal for research is to build an artificial pancreas. Ideally, this would be a mechanical insulin-delivery system that could monitor a patient's blood glucose levels continuously, and would respond by releasing appropriate amounts of insulin, as needed, in much the same way as a healthy pancreas. Such a system would spare patients from painful finger sticks to check glucose levels and from administering insulin injections or monitoring an insulin pump. It would also greatly decrease the risk of severe low blood glucose episodes while improving glucose control, thus reducing long-term complications. While development of an artificial pancreas will require time and careful testing, researchers are rapidly exploiting technologies and tools necessary for such a system, including the very new methods for continuously monitoring blood glucose levels.

Severe hypoglycemia is an acute and potentially deadly risk of insulin therapy. Thus, until it is possible to prevent, reverse, or cure type 1 diabetes in medical practice, a high-priority research goal remains the development of better means of controlling and preventing low blood glucose episodes in patients whose lives are dependent upon insulin therapy.

The Beauregard Family:

What It Is Like To Care for a Young Child with Type 1 Diabetes

The day after two-and-a-half-year-old Hannah Beauregard was diagnosed with type 1 diabetes, her parents, Doug and Mary, were being trained at their local hospital by a team of medical personnel on how to measure Hannah's blood sugar level. Blood sugar is measured in milligrams per deciliter of blood. Although people with diabetes have higher than normal blood sugar levels, they can also occasionally experience dangerous episodes of seriously low blood sugar. "At one point," Doug recalls, "I told the medical team that I must be doing something wrong because the monitor read 20 (milligrams per deciliter)." The proper target range for Hannah, if she hasn't eaten recently, is substantially higher. Before he knew what was happening, attending residents whisked Hannah from his arms and out of her hospital bed into what Doug can only describe as a "little emergency-type" room. "They shut the door and would not allow me in," he vividly recalls.

What Doug didn't know at the time was that Hannah was being administered a medication that acts like "instant sugar." Because Hannah's blood sugar levels had dropped precipitously, this treatment was necessary to prevent her little body from going into a coma. What Doug *did* quickly realize was that having a child with diabetes was going to alter life for the Beauregard family dramatically.

"You Are Not Alone"

Doug Beauregard is a third grade teacher and longtime soccer coach. His wife, Mary, is a registered nurse. Given their professions, one would think that they should know a thing or two about children and medical care—and they do, a great deal. But having a young child with type 1 diabetes is often as difficult for them as it is for anyone else. "You are not alone," Doug wrote recently in an e-mail to another parent seeking advice on how to deal with a toddler with type 1 diabetes who was refusing to eat after taking her insulin. "We're facing the same problem with Hannah."

People with type 1 diabetes must carefully monitor their blood sugar levels throughout the day to determine when they need to eat, and administer insulin, either through injections or an insulin pump, to help their bodies use the sugar from carbohydrates in food. Both steps are also necessary to help keep blood sugar levels within a healthy target range. A constant challenge faced by people with type 1 diabetes is matching food intake, physical activity, and insulin doses in order to maintain healthy blood sugar levels. For example, although too little insulin leads to high blood sugar (hyperglycemia), administering too much insulin for the body's needs at a given time can cause blood sugar levels to fall too low (hypoglycemia). Dramatic rises and drops in blood sugar levels can have immediate and life-threatening consequences, and need to be avoided. Moreover, research has shown that carefully controlling blood sugar levels over the long term is crucial to help prevent serious complications of diabetes, such as diabetic eye, kidney, and nerve disease, and cardiovascular disease.

Controlling Sugar Levels Is a Constant Chess Match

Carefully controlling blood sugar levels, especially in a young child with type 1 diabetes, is no easy task. Just ask the Beauregards.

PATIENT PROFILE

According to Doug, since November 14, 2002, the day Hannah was diagnosed with type 1 diabetes, he and Mary have had few uninterrupted nights of sleep. "If Hannah snores, whimpers, cries, moves, or whatever, we wake up," he says. We can tell by the way she is sleeping if her blood sugar is low or high. "If I think it is low, I will check her. If not, I try to comfort her."

It has now been more than 3 years since Hannah was diagnosed. In that time, the Beauregards have been relatively successful at developing systems for keeping Hannah's blood sugar levels within a normal range, especially at night, when levels tend to drop, a phenomenon called nocturnal hypoglycemia.

To compensate for sugar level drops over the night, Hannah's parents try to put her to bed with a high enough blood sugar level so that she will wake up in the normal range. At least that's the goal, but it's a lot easier said than done. "It's a constant chess match," says Doug. "Her body makes a move; we make a counter move."

For example, physical activities tend to decrease blood sugar levels. Hannah's activities, like playing soccer, end about 7:00 p.m. To bring her sugar level up before she goes to bed, which is around 9:30 p.m., the Beauregards usually give Hannah a snack—a fruit snack, sometimes followed by a protein-rich food.

"There are many nights, however, when Hannah will wake up, get out of bed, and tell us she's hungry," says Mary. "I'll check her levels and find that she's in a low but not dangerous range. I'll give her something to bring her level up a bit so she can safely get through the night. It's as if her body is talking to her and telling her what she needs."

But there are no hard and fast rules to this chess game. Hannah can go to bed with an acceptable blood sugar level on one night and wake up with a higher sugar level, but on another night, she might wake up with very low blood sugar, even if she started at the same point.

Then there are the real "Sugar Monster" nights when, according to Doug, there are no obvious reasons why Hannah's blood sugar will surge. Last Spring, for example, Hannah lay in her bed crying uncontrollably, with a very high blood sugar level. Doug gave her extra insulin to bring her level down, and 15 minutes later she stopped crying, was peaceful and sound asleep. "But we worried about her all night and wondered what her numbers would be like in the morning," says Doug. In addition, the Beauregards run the battle of having to prick Hannah's little fingers yet again to test her sugar levels—fingers that have already been pricked thousands of times. "It's a question of whether we have faith in what we did," says Doug. "Controlling Hannah's sugar is really an art, not a science, and there are days I wish we didn't have to go through all of this," adds Doug.

When Hannah reminded her bear Rufus that it was time for his evening shot, she was really announcing to her parents that she was ready to have her own shot. The lesson: If Rufus can do it, Hannah can do it, too.

As a result of such diligence, Hannah's hemoglobin A1c (HbA1c) tests have nearly always been good, between 6.9 and 7.1, which lowers Hannah's risk for complications from type 1 diabetes. These tests are administered by her endocrinologist and are a good indicator of average blood sugar levels over a 3-month period.

It's obvious that Doug and Mary love Hannah dearly. Doug, in particular, has made it his mission to tell everyone he can about Hannah and how special she is. "No one is responsible for Hannah's having type 1 diabetes. It's just part of her life, and we love her for who she is," says Doug, who actively tries to help other parents whose children have this life-threatening disease.

In many ways, Doug is the consummate communicator. The very first night that Hannah was diagnosed, Doug was on the Internet searching for local support groups. Today, their family attends a support group near their hometown of Plainwell, Michigan. The group consists of families of children with type 1 diabetes who range

in age from 2 to 13 years old. Doug also frequently exchanges e-mails with people around the world, from Argentina to Newfoundland. "We are all seeking answers for our children," says Doug. "We learn a lot through each other's experiences and mistakes."

What About All of Those Finger Pricks and Shots?

It is hard enough for adults with type 1 diabetes to take all of the steps necessary to take care of their disease. Therefore, the questions remain: How does a parent convince a small child with type 1 diabetes that enduring finger pricks to test blood sugar levels and shots to administer insulin, several times a day, is necessary in order to stay alive and healthy? How do parents feel about having to administer those finger pricks and shots?

To help the whole family adjust to Hannah's new health needs, the Beauregards introduced Hannah to a friend—a fluffy brown teddy bear named Rufus. Rufus™, The Bear with Diabetes, was given to Hannah by the organization Childrenwithdiabetes.com. Within hours of their meeting, Rufus became Hannah's fast friend. Rufus is designed so that he, too, needs to have his fingers "pricked" and to be given "shots." It wasn't long before Hannah was administering "shots" to Rufus. After finger pricks to test for sugar levels, both Hannah and Rufus would have their fingers wiped and a special Band-Aid applied. When Hannah reminded her bear Rufus that it was time for his evening shot, she was really announcing to her parents that she was ready to have her own shot. The lesson: If Rufus can do it, Hannah can do it, too.

Everyone in Hannah's family—except 2-year-old Evan—knows how to care for her, including her 14-year-old brother, Ryan. "Ryan is really good with his little sister," says Mary. "Yes, they fight and can drive us crazy at times, but Ryan and members of his soccer team know how to test Hannah's blood sugar level," adds Doug.

The good news is that the older Hannah gets, the more choices she can make for herself to help balance her diet, physical activities, and insulin injections so that she can maintain healthy control of her blood sugar levels. As Hannah becomes more independent, it is becoming easier for her parents. Doug recounted an experience in which he encouraged Hannah in learning about the foods she needs to eat in order to obtain the proper amounts and balance of nutrients she requires at each meal, including carbohydrates. Says Doug, "At dinner the other day, Hannah said she was full. I told her that she needed to eat so she would get her carbs (carbohydrates). Hannah then asked, 'Dad, does my bread have carbs?' Yes, I told her. 'How about my meat?' No, I said. 'I guess I will eat my bread then,' she said." Hannah recognized the need to have her carbohydrates to stay healthy. The Beauregards try to make Hannah feel in control of her diabetes as much as possible by giving her choices. "We also always have a fallback food just in case Hannah doesn't want to eat what we have for dinner," Mary adds.

As much as Doug and Mary sometimes feel they have things pretty much under control, "It's not easy being a parent of a child with diabetes, and it never will be," Doug says. The kindergarten Hannah attends, for example, was leery at first about having a student with Hannah's disease, so the Beauregards had to educate the staff about diabetes and what to do if Hannah's blood sugar level became too low or too high. "Part of the problem," says Doug, "is that Hannah isn't always cooperative when her blood sugar level is low." The family has shied away from day care. When Hannah was not in pre-school, Doug's mother, Elizabeth—who is as well trained as Doug and Mary in how to care for Hannah—spent 2 or 3 days a week at the Beauregard home. Doug

> ***"Because Hannah is doing well, we want to get her story out to people. We feel we have something that we might be able to offer to other parents who are struggling with children who have this disease. It gives us strength."***

adds that when he is at work "my students know that if my cell phone rings, it's something important."

In short, life is a constant vigil.

Hannah is growing up to be an adorable little girl whose life will be in constant jeopardy until a cure is found for her type 1 diabetes. Until then, she will be required to take insulin every day of her life to survive.

"We're not angry that Hannah has (type 1) diabetes," says Doug. He and Mary just want to tell everyone they can about their little girl. "Because Hannah is doing well, we want to get her story out to people. We feel we have something that we might be able to offer to other parents who are struggling with children who have this disease. It gives us strength."

"We need to be strong for every child with diabetes," says Doug, "because without their parents, they won't make it."

Hope Through Research

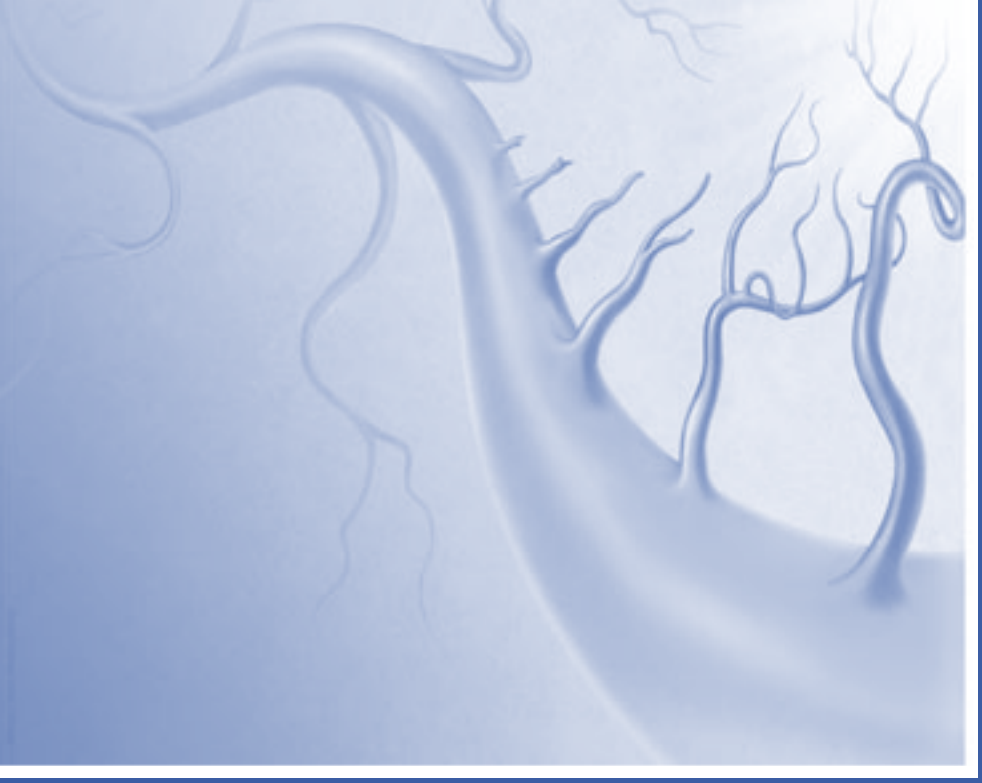
To balance the long-term risks of developing complications associated with hyperglycemia with the short-term dangers of hypoglycemia, patients with type 1 diabetes and their families must perpetually face a chess match of measuring sugar levels and reacting to them with insulin or sugar. The opportunities identified in this chapter of the Strategic Plan outline multiple avenues of research that could help patients avoid hypoglycemia.

As a result of insulin therapy for type 1 diabetes, many patients experience low blood sugar at night during sleep, a phenomenon known as nocturnal hypoglycemia. Sleep can be a particularly dangerous time because it inhibits the normal adrenaline responses that are usually triggered when blood sugar drops below a threshold level; the adrenaline and nervous system responses are needed to warn patients that they are in danger. Nearly half of all episodes of severe hypoglycemia occur during sleep and, in extreme cases, can lead to coma or seizures that can result in fatal cardiac arrhythmia (disturbed heartbeat).

Despite measuring blood sugar levels just before sleep, type 1 diabetes patients often find it difficult to predict the profile of blood sugar during the night. Research that explores the relationship among diet, behavior, insulin therapy, and the nocturnal sugar profile will make it easier to predict and prepare for changes in blood sugar during the night. For example, preliminary results from the Diabetes Research in Children Network (DirecNet) indicate that the timing of exercise during the day corresponds to the level to which blood sugar drops during the night. Relevant research that is under way or that is recommended in this Strategic Plan includes:

- Developing minimally invasive glucose sensors to facilitate continuous glucose monitoring, even while the patient is asleep;
- Mapping nocturnal glucose profiles to behaviors such as exercising before bed;
- Improving algorithms that allow patients to optimize long-lasting and short-acting insulin analogues;
- Closing the loop: developing an artificial pancreas that monitors blood sugar and automatically delivers insulin; and
- Determining the effects of hypoglycemia on long-term brain function.

Figure Legend: Angiogenesis, the branching and extension of existing blood vessels, is integral to development of the blood vessel system (vasculature) in both the embryo and adult. Some diabetes complications (e.g., nerve damage) may be treated by *stimulating* angiogenesis, whereas other complications (e.g., retinopathy) may be treated by *inhibiting* angiogenesis.



GOAL V:

PREVENT OR REDUCE THE COMPLICATIONS OF TYPE 1 DIABETES

Why It Is Important To Prevent or Reduce The Complications of Type 1 Diabetes

Destructive Complications of Type 1 Diabetes

Identifying Targets for New Diagnostics and Therapies—Learning How Diabetes Leads to Complications

- Insulin Deficiency
- Elevated Blood Glucose
- Mechanisms by Which Hyperglycemia Causes Damage
- Additional Targets for Therapeutics Development—Blood Vessel Damage and Repair Pathways, Inflammation, and Abnormal Lipid Processing
- Finding New Therapeutics
- Facilitating Clinical Trials Using "Biomarkers" as Early Molecular Signs of Diabetic Complications

Predicting Risk of Complications

A Brighter Future

Patient Profile

Dana Lewis: Teen on a Mission To Help People with Type 1 Diabetes

WHY IT IS IMPORTANT TO PREVENT OR REDUCE THE COMPLICATIONS OF TYPE 1 DIABETES

The constant companion of people with diabetes and their loved ones is fear of the complications of the disease. The newly diagnosed patient asks: "If my average blood glucose level is good, how dangerous is the occasional high? Will my vision be impaired? What about my kidneys? Can I be tested to find out my risk of developing complications?" Patients who already have one or more of the complications ask: "What, if anything, can I do to limit the damage that diabetes is causing to my body?"

Type 1 diabetes ravages nearly every part of the body: the heart, eyes, kidneys, nerves, lower limbs, mouth, and digestive and urologic systems. It can also ravage the emotional well-being of individuals with diabetes and their families and loved ones. Avoiding acute, life-threatening hypoglycemia and ketoacidosis is a daily concern for people with type 1 diabetes and their families. These daily worries are compounded by the fear of the tissue-damaging chronic complications that might strike in the future.

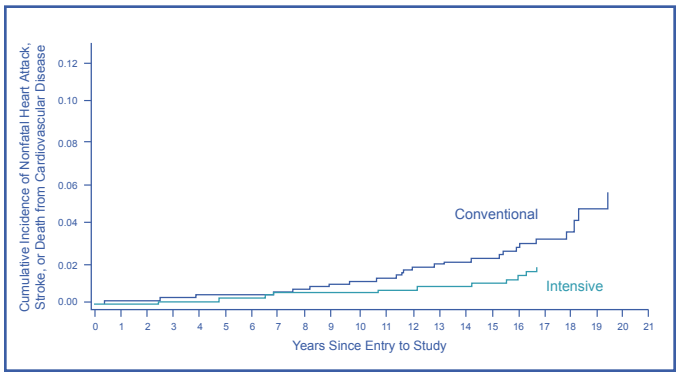
Destructive Complications of Type 1 Diabetes

Improved therapy has significantly increased life expectancy for people with type 1 diabetes in recent decades. Nonetheless, life expectancy may still be shortened by about 15 years (4), with heart attacks and strokes ranking as the primary cause of premature death (5). Cardiovascular disease strikes people with type 1 diabetes at 10-fold greater rates compared to people in the age-matched general population (2, 3); and treatment is particularly difficult because the effects of type 1 diabetes reduce the success of established cardiovascular therapies. The daily lives of many people with type 1 diabetes are made harder as a result of vision loss from diabetes. Patients with diabetes also face increased risk of irreversible kidney disease (end-stage renal disease), leading to the requirement for either dialysis for the remainder of their lives or a kidney transplant.

Amputation of the lower extremities is too frequently the end result of nonhealing foot ulcers. Patients with diabetes can lose sensation in the legs and feet because of diabetic nerve damage. The consequent inability to perceive pain allows the silent development of foot ulcers, which then fail to heal because of insufficient blood flow and other factors secondary to diabetes.

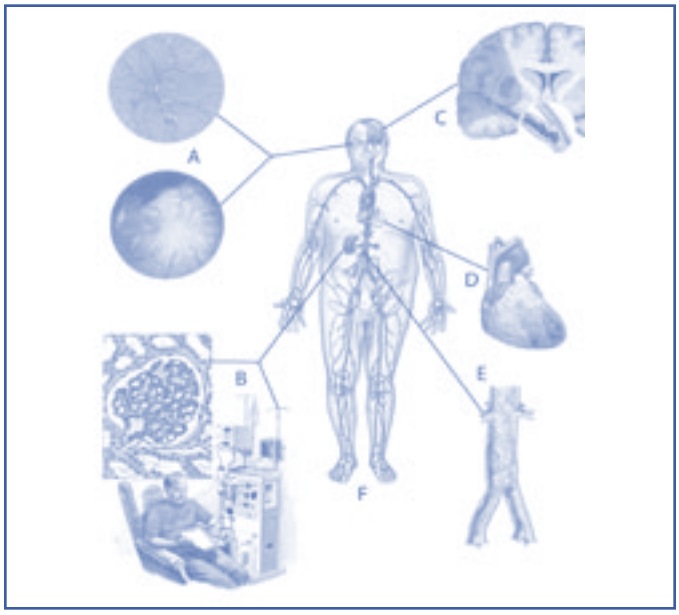
Among other complications of this disease are erectile dysfunction, urinary incontinence, nocturnal diarrhea, gum disease, and other oral health problems. Women with type 1 diabetes face additional health risks during pregnancy, and diabetes is associated with increased risk of birth defects in their children. Diabetes and its complications can lead to depression, poor quality of life, and family conflict. These difficulties can contribute to poor regimen adherence, accelerating the devastating complications of diabetes.

Until the prevention or cure of type 1 diabetes becomes possible, intensified research toward preventing and treating the complications of the disease is critically important. In addition to providing overwhelming benefits for people



Intensive treatment of type 1 diabetes, which includes four or more glucose measurements and three or more insulin injections daily, has been shown to reduce the onset and progression of complications. Results from the DCCT/EDIC research study have recently demonstrated that intensive treatment can reduce the risk of heart attack, stroke, or death from cardiovascular disease by 57 percent compared to conventional treatment.

(Image courtesy of Dr. David Nathan and adapted with permission from Nathan DM, et al. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. N. Engl. J. Med. 353: 2643-2653. Copyright © 2005 Massachusetts Medical Society. All rights reserved.)



Type 1 diabetes is associated with serious medical complications. These complications can negatively affect the body in a variety of ways and include: (A) blindness; (B) kidney disease; (C) stroke; (D) heart disease; (E) atherosclerosis (clogged arteries); and (F) nerve damage leading to foot ulcers and amputation.

(Illustration credit: F. Netter, MD, C. Machado, MD, and ICON Learning Systems. Netter medical illustration adapted with permission of Elsevier. All rights reserved.)

with type 1 diabetes, this research would improve the lives of the millions of Americans with type 2 diabetes, who suffer many of the same complications.

Identifying Targets for New Diagnostics and Therapies—Learning How Diabetes Leads to Complications

***Insulin Deficiency*:** The path from the onset of type 1 diabetes to the development of severe complications begins with insulin deficiency. Researchers are vigorously working to devise ways of replenishing the insulin-producing cells that are destroyed by type 1 diabetes, as described in Goal III. However, because of the extraordinary complexity of replacing or regenerating these cells, scientists are also accelerating research to target other points along the path from diabetes to its complications.

***Elevated Blood Glucose*:** One immediate result of insulin deficiency is high blood glucose levels, termed "hyperglycemia," a hallmark of type 1 diabetes. Scientists have demonstrated that intensive control of blood glucose levels can have long-lasting effects toward reducing the onset and progression of complications. Such intensive glucose control was achieved by type 1 diabetes patients in the landmark Diabetes Control and Complications Trial (DCCT), through more frequent monitoring of blood glucose levels than was conventional, along with more frequent insulin injections or use of a pump. The intensively treated group had dramatic drops in eye, kidney, and nerve disease. In an ongoing follow-up effort, the Epidemiology of Diabetes Interventions and Complications (EDIC) study, researchers are continuing to evaluate the health of the DCCT participants, both those who had been assigned to intensive treatment and those in the conventional treatment control group. After the DCCT ended, those in the conventional group improved their glucose control, but the individuals who had been in the intensive treatment group were unable to maintain such strict control of their blood glucose levels. During the decade following the trial, glucose control was similar in both groups. Surprisingly and provocatively, however, the effects of a finite time of intensive control have persisted for years. In fact, the difference in rates of development of complications between DCCT participants in the intensive and conventional groups has continued to widen. Compared to the DCCT participants from the conventional treatment group, those who were in the original intensive treatment group continue to have a lower incidence of complications—eye and kidney disease, heart attacks, and stroke—even 10 years later, despite similar levels of glucose during this period. In contrast, the effects of higher glucose exposure for a finite time in the DCCT participants from the conventional group have also persisted, causing increased complication rates, despite long-term improvement of hyperglycemia. The phenomenon of long-lasting effects of a period of intensive or nonintensive glucose control is termed "metabolic memory." The discovery of the molecular and cellular basis of metabolic memory is urgently needed so that therapies can be designed to mimic or induce the body's protective "memory" of good control of blood glucose levels and to counteract the harmful "memory" of higher glucose levels.

***Mechanisms by Which Hyperglycemia Causes Damage*:** In addition to lowering blood glucose, another strategy for blocking the path from type 1 diabetes to its complications is to impede the processes by which high glucose levels cause cell and tissue damage. Pursuing this approach, scientists have recently suggested that a variety of deleterious molecular effects of diabetes may all arise from a single, hyperglycemia-induced process: the overproduction of a molecule called superoxide. Several novel agents based on this pathway have shown promise in pre-clinical experiments and should be evaluated in clinical studies in type 1 diabetes patients.

***Additional Targets for Therapeutics Development—Blood Vessel Damage and Repair Pathways, Inflammation, and Abnormal Lipid Processing*:** Other advances in understanding the molecular events leading to diabetic complications will spur the design

of potential new therapies. For example, a key aspect of diabetic complications is the underlying damage to blood vessels throughout the body. Scientists recently found that diabetes not only leads to blood vessel damage, but also may impair the regeneration of healthy new blood vessels. Novel drug- or cell-based therapies to induce new blood vessel growth (angiogenesis) in type 1 diabetes patients may help promote wound healing and assist with repair of diabetes-induced damage to the heart and nerves. In contrast, excessive angiogenesis contributes to diabetic eye disease; thus, limiting new blood vessel growth in the eye may be beneficial. Cancer researchers have developed effective new cancer drugs targeted at angiogenesis. The role of such new therapeutics in slowing or reversing diabetes complications is under active investigation. Other researchers are focusing on the abnormal metabolism of fats in type 1 diabetes, including the toxic accumulation of fatty acid molecules in heart cells and the activation of molecular pathways related to inflammation, which also provides opportunities for intervention.

***Finding New Therapeutics*:** An approach pioneered in the NIH Roadmap for Medical Research provides a new strategy to accelerate the discovery of therapeutics for diabetes complications. "High-throughput screening" refers to the testing of large numbers of compounds (i.e., a library) to see whether any show promise as potential drugs. Screening for therapeutic drugs requires biological assays that can be performed rapidly in the laboratory and reflect what is happening in the body as complications develop. Compounds identified as potentially useful by a high-throughput screen for diabetic complications can then be more intensively investigated to choose the most promising candidates for clinical trials. A crucial step in this selection process is testing compounds in animal models for diabetic complications. Suitable animal models that mimic the human condition are critical for the success of drug development. Efforts are under way to create such models by drawing upon new understanding of the molecular pathways underlying development of complications.

***Facilitating Clinical Trials Using "Biomarkers" as Early Molecular Signs of Diabetic Complications*:** The multi-organ damage caused by type 1 diabetes progresses silently for many years before signs or symptoms become apparent. Even more years may elapse before complications reach the severity of a heart attack, kidney failure, or other devastating event. Very early detection of the development of complications could permit early, successful intervention and reduced suffering for type 1 diabetes patients. Thus, a critical area for research is the discovery and evaluation of "biomarkers" for early detection of damage to cells and tissues. For example, the abnormal excretion of small amounts of protein in urine is currently used as a biomarker for early diabetic kidney disease, before organ deterioration to kidney failure. Early intervention based on this biomarker has been credited with the recent slowing in rates of kidney failure in the United States. The molecular processes along the path from insulin deficiency to development of complications, discussed earlier, present rich opportunities for the discovery of new biomarkers. Scientists are also exploring noninvasive imaging techniques as a means of detecting disease progression.

Biomarkers research will also facilitate and expedite clinical trials. The development of therapeutics for diabetic complications is severely constrained because of the relatively slow progression rate of these complications. Therefore, clinical trials must extend for long durations for researchers to detect the effect of a candidate drug. "Surrogate endpoints" are biomarkers that are strongly associated with and predictive of disease outcomes. Valid surrogate endpoints can be used in shorter clinical trials to choose the most promising drug and trial conditions, prior to longer clinical trials assessing the definitive clinical endpoint. However, the standards for acceptance of new biomarkers and surrogate endpoints are extremely high, adding to the challenges of this area of research.

Predicting Risk of Complications

The occurrence and progression of diabetic complications vary markedly among patients. Many factors contribute to the risk for complications, including genetic variation. Several research consortia are conducting studies to identify genetic factors that confer susceptibility or resistance to diabetic complications, including the Genetics of Kidneys in Diabetes Study (GoKinD) and the Family Investigation of Nephropathy and Diabetes Study (FIND), as well as a component of the EDIC study. Results of this research may help to inform patient care, advance the discovery of new mechanisms of disease progression, and aid the development of potential new therapeutics. In addition, research on the behavioral, emotional, and family systems processes by which people with type 1 diabetes experience barriers to self-care may help to identify patients at high risk of developing complications and to test interventions that can improve their adherence to treatment regimens.

A Brighter Future

The prognosis for people with type 1 diabetes is steadily improving, yet the disease continues to exact a devastating toll. By elucidating the cellular and molecular processes by which type 1 diabetes progresses to complications, and by propelling research on detection methods and advanced techniques for drug development, scientists will greatly improve the lives of people with this disease. These efforts will further reduce the heightened risk for heart disease, kidney failure, blindness, and other debilitating, costly, and deadly complications of diabetes. A great hope of this research is that children and adults with type 1 diabetes today will have a much brighter future.

Dana Lewis:

Teen on a Mission To Help People with Type 1 Diabetes

Dana Lewis, of Huntsville, Alabama, is on a mission.

A self-proclaimed "good talker," Dana began speaking at American Diabetes Association (ADA) events on behalf of people with type 1 diabetes shortly after she was diagnosed with the disease at age 14. Two years later, she was ADA's Alabama Ambassador.

> ***Dana's message is simple and clear to people with type 1 diabetes: "The number one priority is to take good care of yourself and to maintain good blood sugar levels... and don't let diabetes get you down," she exclaims, "it's a disease we can control."***

Today, 17-year-old Dana crisscrosses the United States as ADA's 2005-2006 National Youth Advocate. She meets with policy makers to increase awareness of type 1 diabetes, and reaches out to her peers, as well as adults, to encourage them to become involved in the fight against diabetes.

Dana's message is simple and clear to people with type 1 diabetes: "The number one priority is to take good care of yourself and to maintain good blood sugar levels...and don't let diabetes get you down," she exclaims, "it's a disease we can control."

Dana is also a strong advocate for helping others through volunteerism. "No matter what you do," she says, "doing something for someone else is better for you than anything else. Volunteering is what puts diabetes in perspective for me."

But getting to this point wasn't easy, even for this dynamic teen.

A Teenager with Type 1 Diabetes

Dana was a high school freshman when she was diagnosed with type 1 diabetes. She says she was "scared" of diabetes because her grandmother had been diagnosed with the type 2 form of the disease when Dana was 9 or 10 years old. Dana knew that type 1 and type 2 diabetes are not the same. It took her a while to get used to being "different" from everyone else. "Diabetes was a curse word to me," she says, "and I didn't want to tell anyone that I had it."

Except for sharing with a few very close friends, Dana kept the fact that she had type 1 diabetes a secret from others for 4 or 5 months after her diagnosis. Then one day, when she was in her advanced geometry class, Dana suddenly made a complete turnaround. "I just all of a sudden said to myself that I want to get an insulin pump; I want to find a cure for this disease, possibly as a doctor or a researcher; I want to do whatever I can." Dana is currently considering majoring in biomedical engineering when she enters college.

In the meantime, she stays focused on her mission of keeping herself healthy, helping others, and advocating for a cure for type 1 diabetes.

PATIENT PROFILE

Taking Care of Herself

As captain of her high school's color guard, Dana leads the group in its four to five practices a week. She says she loves being part of the color guard because, "It's a fun way to exercise." She also likes to take walks around her neighborhood with her family, ride bikes with her friends, and play percussion instruments in her school band, which, she says, is also very physical. "Exercise may seem like work, but it can also be fun," says the vivacious, articulate Dana.

Dana is acutely aware that exercising, eating the right foods, and testing her blood sugar levels numerous times a day help to keep her blood sugar level in the normal range. Tight regulation of blood sugar levels helps to prevent or delay the development of life-threatening disease complications, such as diabetic eye, kidney, nerve, and heart disease.

Diabetes has put Dana very much in touch with her body and herself. "I find that when I get stressed, my blood sugar goes up." To help prevent this problem, she spends part of every day by herself, just relaxing, perhaps reading or writing, which are two of her favorite things. To control her blood sugar levels, Dana also uses an insulin pump and is meticulous about checking her blood sugar levels. "I test (my blood sugar), on average, 10 to 12 times a day, and I'm careful about counting my carbs (carbohydrates)," she says.

Dana is acutely aware that exercising, eating the right foods, and testing her blood sugar levels numerous times a day help to keep her blood sugar level in the normal range. Tight regulation of blood sugar levels helps to prevent or delay the development of life-threatening disease complications, such as diabetic eye, kidney, nerve, and heart disease.

"It's *really* important for me to take good care of myself." Yet, part of Dana's mission is to take good care of others, as well.

Taking Care of Others

To help teens like herself, Dana created a support group, called "Teen Team," which serves as a venue for members to share their experiences. "Support groups provide an opportunity to meet other teens who have diabetes and to learn how they are managing and juggling the disease with everything else that's going on in their busy lives," she says. She encourages young people to contact a local diabetes education center or doctor's office to help get a support group up and running in their school or community.

In addition to leading her support group, Dana gives presentations on diabetes in her human anatomy and physiology classes. "It gives me a platform to inform my peers about my disease. All my friends know exactly what to do to help me if my blood sugar suddenly gets too high or too low."

This past summer, Dana traveled to more than 10 states and met "so many kids" with diabetes to whom she always brings her important messages of: (1) keep your blood sugar levels in normal range; and (2) never give up on yourself because you have diabetes. The best thing about these encounters is that Dana gets as much out of them as the young people with whom she interacts. "It's truly inspirational for me when I meet these kids. Being an ADA youth advocate has been an incredible experience," says Dana.

Trying To Take Care of the Future

Although she has two older brothers, Dana is the only member of her family diagnosed with type 1 diabetes. "My mom keeps a close watch on my brothers for any symptoms, but so far they are diabetes-free," says Dana.

Even at such a young age, Dana knows that little will change for type 1 diabetes patients unless more research is done. Dana is doing everything she can to get the word out.

She already has met with several congressional leaders and has written a number of articles that have been published in her hometown newspaper—all to bring attention to type 1 diabetes. She continues to speak at ADA events, and encourages people to participate in America's Walk for Diabetes and the Tour de Cure to help find a cure for the disease.

Despite all of her self-help and advocacy work, Dana harbors a great personal fear.

"I'm working very hard and trying to get a lot of things done, and if something should happen to me, I'm worried that things may fall through the cracks. That's why I'm encouraging as many young people as I can to get involved in the fight against diabetes."

Thankfully, Dana is healthy and active right now. "Even though I have diabetes, I am still Dana, a senior captain of my high school's color guard. I live my life the way I do in spite of having diabetes, not because of it! I plan to make a difference in the fight against diabetes." And she would like nothing more than for others to join her.

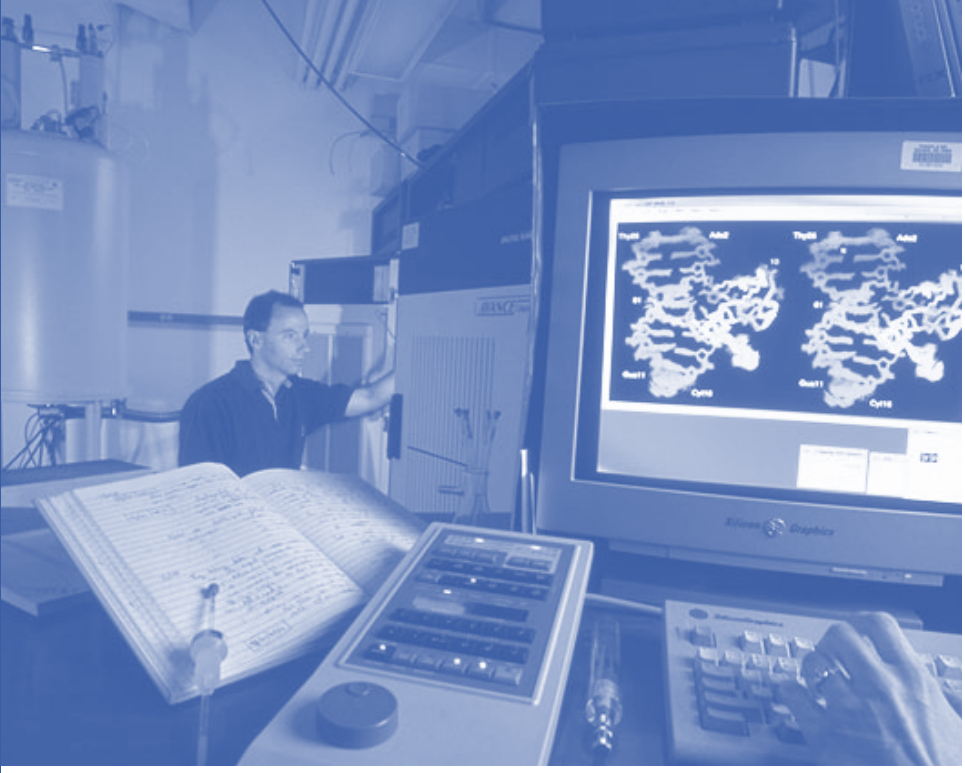
How Research Helps Patients

Patients with type 1 diabetes, such as Dana, have benefited from the results of a landmark NIH-supported research study, the Diabetes Control and Complications Trial (DCCT). Completed in 1993, the trial compared the relationship between intensive versus conventional treatment of blood sugar levels and the development of disease complications in adults with type 1 diabetes. The DCCT proved conclusively that intensive therapy reduces the risk of microvascular (small blood vessel) complications, such as diabetic eye, kidney, and nerve disease. Nearly all patients who participated in the DCCT volunteered to continue to be followed in the Epidemiology of Diabetes Interventions and Complications Study (EDIC), which began in 1994. The DCCT/EDIC researchers continue to report remarkable long-term benefits of intensive blood sugar control in preventing or delaying complications of the eyes, kidneys, and nerves. Important recent findings have demonstrated the value of intensive therapy in preventing damage to large blood vessels in diabetes patients—damage that can lead to heart attacks and strokes. These findings are significant because two-thirds of patients with diabetes die of cardiovascular disease. The dramatic, positive results of DCCT/EDIC have had a profound impact on clinical practice for the management of type 1 diabetes: they led to the development of clinical guidelines by the ADA and other groups; spurred the creation of the National Diabetes Education Program (NDEP) to disseminate the findings to the public (www.ndep.nih.gov); and stimulated multifaceted research efforts to develop tools and therapies that enable patients to achieve tight control of blood sugar levels.

"Even though I have diabetes, I am still Dana, a senior captain of my high school's color guard. I live my life the way I do in spite of having diabetes, not because of it! I plan to make a difference in the fight against diabetes."

Because of the limitations and difficulties of current therapies and technologies for achieving good blood sugar control, the NIH is also vigorously pursuing research to increase understanding of the underlying molecular mechanisms of diabetes complications and potential behavioral interventions to develop new therapeutic approaches. The identification of new prevention and treatment strategies for diabetes complications has the potential to not only dramatically improve quality of life for Dana and other type 1 diabetes patients, but also for patients with type 2 diabetes, who suffer from similar disease complications.

Figure Legend: New technologies are helping to accelerate research on type 1 diabetes. *(Photo credit: Richard Nowitz for NIDDK.)*



GOAL VI:

ATTRACT NEW TALENT AND APPLY NEW TECHNOLOGIES TO RESEARCH ON TYPE 1 DIABETES

Why It Is Important To Attract New Talent and Apply New Technologies to Research

Attracting New Talent To Tackle Research on Type 1 Diabetes

- Recruit Experts in Diverse Fields and Train New Researchers
- Collaborative Research

Applying New and Emerging Technologies to Type 1 Diabetes Research

- Visualizing Islets in the Body
- Technology for Identifying Disease Genes
- Studying Proteins Involved in Disease Onset and Progression
- Application of Engineering Principles
- Animal Models To Study Type 1 Diabetes
- Gene Therapy Approaches
- Collection and Analysis of Scientific Data
- Communication Technology

Moving the Research Agenda Forward

Investigator Profile

Andrew Norris, M.D., Ph.D.—Research in Pediatric Endocrinology: Road to Independence

WHY IT IS IMPORTANT TO ATTRACT NEW TALENT AND APPLY NEW TECHNOLOGIES TO RESEARCH

Type 1 diabetes patients and family members may ask: "How will research help me? Will someone invent instruments to test glucose levels without painful finger sticks? Are there tests that can catch diabetes complications at an early stage?" Simply put, research is the key to a cure for type 1 diabetes. It was through research efforts in the early 1900s that scientists discovered insulin and started using it to save the lives of type 1 diabetes patients. It was also through research that improvements in disease monitoring and treatment strategies have been achieved. These advances have contributed to significant improvements in patients' health and quality of life. Only through research efforts will a real cure for this disease be realized.

Attracting New Talent To Tackle Research on Type 1 Diabetes

Harnessing new and emerging technologies, as well as pursuing all of the future research directions described in this Strategic Plan, is dependent on the existence of a workforce of talented researchers with diverse expertise. The NIH has been proactive in developing research programs, supported by the *Special Statutory Funding Program for Type 1 Diabetes Research*, to attract creative, skilled scientists to study type 1 diabetes and its complications, and to empower them to conduct their research through access to cutting-edge tools and technologies. Research initiatives and mechanisms designed for type 1 diabetes should continue to serve as a model for NIH in exploring how to translate discovery research into health gains.

***Recruit Experts in Diverse Fields and Train New Researchers*:** Type 1 diabetes affects many different organ systems (e.g., pancreas, eyes, kidneys, heart, nervous system) and involves diverse areas of science (e.g., immunology, stem cell and developmental biology, bioengineering, behavioral research) and medicine (e.g., pediatrics, transplant surgery). Therefore, it is imperative to pursue research on all of these different areas to have the greatest impact on the health of patients. Experienced researchers with a particular expertise (e.g., immunology, heart disease, eye disease) should be recruited to apply their talents to research on type 1 diabetes. Researchers with expertise in many of the newest technologies should also be recruited to apply these sophisticated tools to further understanding of the disease. Moreover, it is important to train and retain new scientists and clinicians to sustain momentum in the field.

The NIH promotes the translation of fundamental discoveries from the laboratory bench of basic scientists (below) into investigations in the clinic (opposite), which promise to directly benefit type 1 diabetes patients.

(Photo credit: Below—third photo from left: Richard Nowitz for NIDDK; other photos: Getty Images. Opposite—Richard Nowitz for NIDDK.)

***Collaborative Research*:** Increasingly, multidisciplinary teams of investigators must pool their expertise to catalyze research progress. Because researchers in a particular technology or research area may not have expertise in type 1 diabetes, they must be encouraged to work with scientists who have knowledge of the disease. These types of partnerships can truly synergize research efforts and reap tremendous benefits for patients.

Applying New and Emerging Technologies to Type 1 Diabetes Research

The tools of biomedical research have evolved rapidly due to the biotechnology revolution. Many technologies that were used 20 years ago have been replaced by new technologies that permit scientists to conduct research more efficiently and to ask and answer questions that were previously impossible to frame. Some new and emerging technologies hold real promise for advancing the type 1 diabetes research field.

***Visualizing Islets in the Body*:** When a person breaks a bone, an x-ray is used to see the injury. This technique makes it much easier for doctors to diagnose the break and effectively treat it. Likewise, it would be useful to "see" a person's islets. Why would this be important? Type 1 diabetes is usually diagnosed late in the disease process, when most of the insulin-producing beta cells have already been destroyed. If researchers could detect islet destruction by visualizing the islets before the onset of clinical symptoms, then they could intervene earlier to try to prevent further islet loss and the need for insulin administration. Furthermore, such a technological breakthrough would make it more efficient to conduct clinical trials, because scientists could actually "see" if a therapy was effective at either preventing or reversing islet loss. Another potentially beneficial application of this technology is to improve outcomes of islet transplantation. If doctors could see when transplanted islets are beginning to be rejected by the immune system, then they could intervene earlier, to prevent graft rejection and the need for patients to resume insulin administration. Recently, significant advances in visualizing islets using techniques such as magnetic resonance imaging (MRI) have been achieved in mouse models. More research in this area is needed to translate these results to humans, in order to overcome this major clinical and research barrier in type 1 diabetes.

***Technology for Identifying Disease Genes*:** With the completion of the Human Genome Project and with new "high-tech" laboratory methods, genetics experiments that once took months now take minutes. These advances will significantly speed the discovery of disease-causing genes, including those that play a role in type 1 diabetes disease onset or the development of complications. Identification of key genes will promote the development of novel prevention strategies.

***Studying Proteins Involved in Disease Onset and Progression*:** Recent research advances have improved scientists' ability to study proteins in the body. Fifteen years ago, researchers were only able to study relatively small numbers of proteins at one time to determine if or how they had a role in disease onset or progression. Because there are tens of thousands of proteins in the body, studying proteins a few at a time is an extremely time-consuming endeavor. However, novel "proteomics" technologies have been developed that now permit researchers to study thousands of proteins at once, as well as to determine how proteins may interact with each other. These technologies can be used, for example, to identify proteins that correlate with stage or rate of progression of type 1 diabetes and its complications. Furthermore, understanding the expression and function of proteins will enhance understanding of the genes by which the proteins are produced. These insights could directly translate into improved disease detection and prevention strategies.

***Application of Engineering Principles*:** There are several areas of type 1 diabetes research that could benefit from the application of engineering principles to disease (bioengineering). For example, identifying ways to measure blood glucose

levels without the need for a finger stick would dramatically improve the quality of life of type 1 diabetes patients. Even more beneficial would be linking such measures to insulin delivery devices to create an artificial pancreas. In the field of islet transplantation, if transplanted cells could be protected from the immune system by some material or device, then there would be a greater chance of transplant success with avoidance of toxic immunosuppressive drugs. To realize these and other advances, it is important to apply bioengineering approaches to type 1 diabetes research.

***Animal Models To Study Type 1 Diabetes*:** Animal models are an important scientific resource because they enable researchers to investigate underlying disease processes that cannot be studied in humans. These models also permit assessment of novel therapeutic interventions before they are tested in people. The use of animal models is a necessary early step to promote translation of research findings from the laboratory to human patients. It is crucial to develop and utilize animal models with greater fidelity to human type 1 diabetes and its complications to propel research progress.

***Gene Therapy Approaches*:** When genes in the body are defective, a plausible treatment strategy is to replace them with those that work properly. Researchers have been exploring novel ways to deliver genes to people or transplanted tissues, through a process called gene therapy. These approaches, once developed, could also be used to benefit type 1 diabetes patients. For example, islets transplanted into a type 1 diabetes patient undergo attack by the immune system, which treats them as foreign invaders. Gene therapy approaches could be used to protect islets from this attack or to deliver genes that enhance islet viability in the transplant site. With future research and scientific breakthroughs, gene therapy approaches could also be used to treat diabetic complications, as well as to replace the insulin that type 1 diabetes patients are no longer capable of producing. Gene delivery approaches are also being used to create animal models for the study of therapies for type 1 diabetes and its complications.

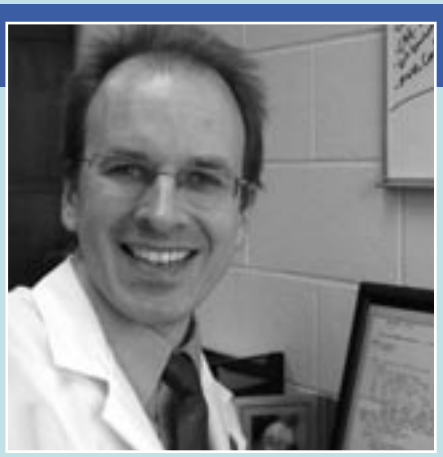
***Collection and Analysis of Scientific Data*:** Because scientists are now collecting more data than they ever thought possible, it has become increasingly important to find ways to assemble, organize, and analyze this valuable information. Furthermore, in order to achieve the greatest impact on the field, scientists must be able to share data with one another, so that they can compare results or combine their efforts to make novel discoveries that they cannot make individually. It is important for researchers to work together and coordinate their efforts in order to accelerate the pace of discovery.

***Communication Technology*:** Patients today have the ability to exchange information with their providers much more easily than ever before. Increased accessibility and improved usability of computers, the Internet, and cellular technology can potentially allow clinicians to be much more involved in frequent monitoring of their patients. Patients can also have access to information and suggested changes in management more quickly and efficiently. Improvements in monitoring technology, and its ability to communicate with a provider's office, can lead to new strategies of case management, higher patient satisfaction, and improved health outcomes.

Moving the Research Agenda Forward

New and emerging technologies, coupled with a cadre of talented scientists, have the potential to bring about real breakthroughs in the understanding, prevention, treatment, and cure of type 1 diabetes. Under the auspices of the *Special Funding Program*, multiple research consortia have been created to tackle specific challenges that will impact the health of people with type 1 diabetes. These efforts bring together clinical and basic researchers, as well as link scientists investigating the pathogenesis and therapy of type 1 diabetes and its complications with new technologies needed to pursue evolving areas of opportunity. New therapies have already had a dramatic impact on extending life and retarding disability from type 1 diabetes. The pace of discovery is accelerating, and, as in the past, future research advances should directly translate into improvements in the health and quality of life of patients. Therefore, it is crucial to deploy new and emerging technologies and to engage experts from diverse fields in the battle to overcome type 1 diabetes and its complications.

This is a new and exciting era of scientific research. Scientists are now able to study biological processes in ways that were not possible even a few short years ago. It is essential to take full advantage of the new technologies and information that have emerged, in order to optimize progress. A talented workforce of researchers must be mobilized to apply their expertise to overcoming current barriers. Type 1 diabetes is a devastating illness for patients and their families, especially when it strikes in infancy, childhood, or adolescence. Pursuing novel research directions and attracting new research talent are key elements in conquering this disease.



Andrew Norris, M.D., Ph.D.

Research in Pediatric Endocrinology: Road to Independence

A Lifelong Ambition

Dr. Andrew Norris always knew that he wanted to be a researcher. "Going into research was a lifelong ambition," recollects Dr. Norris, an Assistant Professor at the University of Iowa. "Beginning in second grade, I read every science book in the library of my elementary school."

Dr. Norris also developed an interest in medicine, so in order to pursue both medicine and research, he enrolled in a combined M.D. and Ph.D. training program at the Washington University School of Medicine in St. Louis. He entered the program intending to pursue medical research, with a particular interest in nutrition and the role that carbohydrates and lipids play in the development of human disease. He also enjoyed working with children. After receiving his degrees, he completed a pediatrics residency program. During that time, more and more children were being diagnosed with type 2 diabetes, and this sparked his interest in studying diabetes, an endocrine disease, in the pediatric population.

For further training as a sub-specialist in pediatric endocrinology, Dr. Norris applied to and was accepted into a combined fellowship program at the Children's Hospital Boston, and the Joslin Diabetes Center. "The fellowship program was an extremely wonderful experience for me," recalls Dr. Norris, "and I went there with the intention of doing diabetes research." During the first year of his fellowship, he worked directly with children with diabetes. "I found that I really enjoyed working with children with diabetes and their families. This positive experience also synergized with my interest in research," states Dr. Norris.

During the next two years of his fellowship, he pursued research in the laboratory of Dr. C. Ronald Kahn, a prominent diabetes researcher. Dr. Norris recalls, "While working in Dr. Kahn's lab, my goal was always to become an independent investigator studying pediatric diabetes." However, making the transition from being a research trainee to an independent investigator can be a daunting task.

Transition to Independence

At the end of his fellowship, Dr. Norris would transition from being a "fellow" to a faculty member, at which time he would be expected to find his own source of funding to support his research program. In preparation for this transition, approximately 1 year before his fellowship ended, he applied for an NIH "Mentored Clinical Scientist Development Award" (K08) to support his research. Two months before becoming a faculty member, he found out that his application was, as he states, "good, but not good enough" to receive funding. Therefore, he was facing the prospect of having to put research on hold until he could find funding support.

Fortunately for Dr. Norris, the Children's Hospital Boston/Joslin Diabetes Center was one of seven sites participating in the NIH-supported "Pediatric Diabetes Research Training and Career Development Program."

Dr. Norris was familiar with this program because, earlier is his fellowship, he was supported by an institutional research training grant (T32) under this umbrella NIH-supported program. In addition to T32 training grants, the program also awards K12 grants (Clinical Scientist Career Development Program), which provide funding for investigators as they transition to independent faculty positions. "Fortunately," says Dr. Norris, "a K12 slot was available when I needed funding to bridge time between completing my fellowship and receiving my own grant. Without the K12 award, I would not have had professional time to pursue diabetes research, and might have instead had no choice but to spend the majority of my time in the clinic. This award mechanism allowed me to have 'protected time' so that I could resubmit my K08 grant application and still focus on diabetes research and building my own research program." While receiving support from the K12 training grant for 1 year, Dr. Norris resubmitted his K08 application and was awarded funding. Importantly, there was no disruption to his diabetes research endeavors.

Dr. Norris has recently joined the faculty at the University of Iowa, where he directs his own independent research program. His research focuses on how the events early in life affect later risk of diabetes and diabetic complications. As an example, a person's blood sugar level today has a strong effect on his or her risk of complications years down the line, even if the individual feels healthy in the interim. In other words, as Dr. Norris states, "The immediate effect is subtle and unnoticed, but over time can lead to significant problems." To this end, he is developing new mathematical models to better identify the early subtle effects of diabetes on gene expression. These tools will help determine how these barely noticeable effects eventually lead to such devastating complications. The hope is to develop improved strategies enabling doctors to better prevent or delay the development of complications, which affect patients with both type 1 and type 2 diabetes. Dr. Norris is also studying the ways that abnormal build-up of fat contributes to the complications of diabetes as well as the development of insulin resistance. This research could provide insights into additional means to prevent or delay certain diabetic complications.

Dr. Norris stresses that, "Because of the shortage of pediatric endocrinologists throughout the country, the pediatric endocrinology research training program is of incredible importance to attracting talented individuals to pursue research in this area." Furthermore, he notes, "It is difficult to secure funding for independent research by the end of a fellowship. The K12 grant mechanism is a necessary tool to bridge the gap between completing research training and pursuing independent research."

Pediatric Diabetes Training Program

To enlarge the pool of pediatric endocrinologists conducting diabetes research, the NIH, in partnership with the ADA and the JDRF, awarded institution-wide research training and career development grants to seven medical centers with strong research programs in childhood diabetes: Children's Hospital Boston/Joslin Diabetes Center, where Dr. Norris received his training; Baylor College of Medicine; University of Colorado; University of Pennsylvania; University of Pittsburgh; Washington University; and Yale University. More information on the program can be found on the NIDDK Web site at: www.niddk.nih.gov/fund/diabetesspecialfunds/train_peddiab.htm.

The awards, through the T32 (institutional research training) and K12 (Clinical Scientist Career Development Program) grant mechanisms of the NIH, provide for 2-3 years of fellowship training, as well as 2-3 additional years of support for junior clinical investigators, for a total of 5-6 years of continuous, uninterrupted research training in diabetes. The funding supports up to five positions at each medical center; each center was free to decide how many of the five slots were to be reserved for pediatric endocrinology fellows or investigators who were transitioning from fellowship to independent scientist.

These T32/K12 awards now support 34 pediatric endocrinology fellows/junior clinical investigators each year, all of whom are receiving research training and career development in many aspects of diabetes research. At the time of this publication, nine pediatric endocrinologists supported by this program have received individual NIH or JDRF career development awards. Moreover, more than five of the trainees were recipients of an award through the NIH Loan Repayment Program that offsets some of the educational debt incurred by many graduates in the health professions. (See: www.lrp.nih.gov)

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APPENDIX A: STRATEGIC PLAN PARTICIPANTS

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APPENDIX B: ACRONYMS AND ABBREVIATIONS

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Organizational Components

ADA	American Diabetes Association
CDC	Centers for Disease Control and Prevention
CMS	Centers for Medicare & Medicaid Services
HHS	Department of Health and Human Services
DMICC	Diabetes Mellitus Interagency Coordinating Committee
FDA	Food and Drug Administration
JDRF	Juvenile Diabetes Research Foundation International
NCRR	National Center for Research Resources
NEI	National Eye Institute
NHGRI	National Human Genome Research Institute
NHLBI	National Heart, Lung, and Blood Institute
NIAID	National Institute of Allergy and Infectious Diseases
NIBIB	National Institute of Biomedical Imaging and Bioengineering
NICHD	National Institute of Child Health and Human Development
NIDA	National Institute on Drug Abuse
NIDCR	National Institute of Dental and Craniofacial Research
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NINDS	National Institute of Neurological Disorders and Stroke
NINR	National Institute of Nursing Research
NLM	National Library of Medicine

Research Programs

AMDCC	Animal Models of Diabetic Complications Consortium
BCBC	Beta Cell Biology Consortium
CIT	Clinical Islet Transplantation Consortium
CITR	Collaborative Islet Transplant Registry
DAISY	Diabetes Autoimmunity Study in the Young
DCCT	Diabetes Control and Complications Trial
DirecNet	Diabetes Research in Children Network
DRCR.net	Diabetic Retinopathy Clinical Research Network
EDIC	Epidemiology of Diabetes Interventions and Complications
FIND	Family Investigation of Nephropathy and Diabetes
GoKinD	Genetics of Kidneys in Diabetes Study
ICRs	Islet Cell Resource Centers
ITN	Immune Tolerance Network
NHPCSG	Non-Human Primate Transplantation Tolerance Cooperative Study Group
SEARCH	Search for Diabetes in Youth Study
T1DGC	Type 1 Diabetes Genetics Consortium
T1D-RAID	Type 1 Diabetes-Rapid Access to Intervention Development
TEDDY	The Environmental Determinants of Diabetes in the Young
TrialNet	Type 1 Diabetes TrialNet
TRIGR	Trial to Reduce IDDM in the Genetically at Risk

Other Acronyms and Abbreviations

DKA	diabetic ketoacidosis
DRI	Diabetes Research Institute
ES cell	embryonic stem cell
ESRD	end-stage renal disease
HAAF	hypoglycemia-associated autonomic failure
HbA1c	hemoglobin A1c
ICA	islet cell autoantibodies
IDDM	insulin-dependent diabetes mellitus
MHC	major histocompatibility complex
MRI	magnetic resonance imaging
NDEP	National Diabetes Education Program

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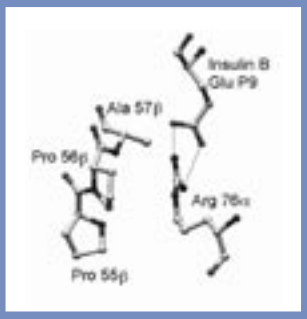

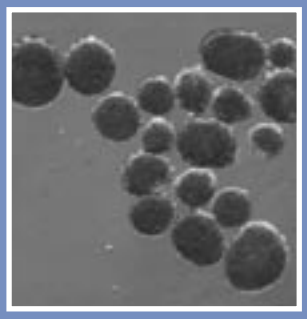

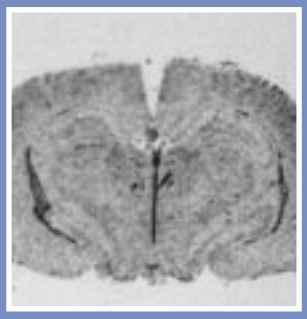

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